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STUDY OF NARCOTICS AND SEDATIVES FOR USE IN PREANESTHETIC MEDICATION

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The use of preanesthetic medication is primarily to produce sedation, but the degree of sedation desirable prior to anesthesia and operation is debatable. Narcotics, while unequaled as analgesics, have many undesirable side-effects. The routine use of narcotics for preoperative medication, therefore, exposes all patients to the hazards of these drugs. There was little difference in the influence of the various preanesthetic drugs on satisfactory induction of anesthesia with any given anesthetic agent, but the complications of the induction period varied according to the preanesthetic drug and the anesthetic agent. The continued routine use of narcotics for preanesthetic medication is unwise and unwarranted. Preoperative medication should be tailored to meet the needs of the patient and his operation.

THE USE OF narcotic and sedative drugs for preanesthetic medication has been the subject of considerable discussion. The proponents of large doses of these drugs vie with advocates of minimal use of depressants. Multiple agents are recommended by some, whereas a single sedative is preferred by others. There have been few factual analyses of the problem with the exception of the report by Cohen and Beecher.[1] The present study was undertaken in order to (*a*) compare the effectiveness of three commonly used narcotics, secobarbital, and a placebo for preanesthetic sedation and (*b*) to determine the incidence of side-reaction to each of these agents and to observe the effect of the drugs upon the conduct of and recovery from anesthesia.

Method

Solutions of the drugs to be tested were dispensed in identical bottles. These were coded and labeled by one individual. An attempt was made to prepare equipotent doses of the drugs. Each milliliter of solution contained morphine, 5 mg.; meperidine (Demerol), 50 mg.; alphaprodine (Nisentil), 30 mg.; secobarbital (Seconal), 75 mg.; or saline solution. The anesthetist or surgical resident ordered the medicament as "blind medication X-ml." If he would normally have ordered 10 mg. of morphine or 100 mg. of meperidine, he would prescribe 2 ml. of the blind medicament. If 5 mg. or 50 mg., he would prescribe 1 ml. The number

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of milliliters selected was based upon clinical judgment. Intramuscular injections were ordered. Neither the person writing for or administering the medicament, the anesthetist, nor the persons compiling the data were aware of the contents of any bottle until after tabulation was complete at the end of the study. All medicaments were given in combination with atropine sulfate.

Blind medication was used in 1,761 patients. This analysis deals with the data recorded from 1,400 patients. The remainder were excluded for the following reasons: scopolamine was used in place of atropine, additional barbiturates were given with the blind medicament, the time interval between injection of medicament and induction of anesthesia was too short (30 minutes or less) or too long (2 hours or more), or the patient was

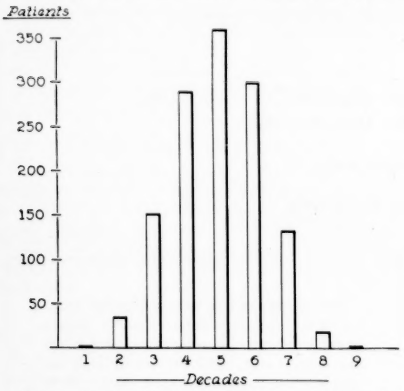

Fig. 1.—Age distribution of 1,400 patients in preanesthetic medication study.

operated on under local anesthesia administered by a surgeon and was not attended by a physician anesthetist.

In the anesthesia room, study sheets were completed by the anesthetist. Vital signs obtained on the ward prior to operation were recorded as well as those obtained just before induction of anesthesia. The preanesthetic condition of the patient was determined according to the following criteria: alert, apprehensive, drowsy, sleeping but easily rousable, and carefree. More than one description could be indicated, but, obviously, alert and drowsy could not be checked simultaneously, nor could apprehensive and carefree. One patient could, however, be alert and carefree, or drowsy and apprehensive. Side-effects such as nausea or vomiting, respiratory depression, dizziness, hypotension, and tachycardia were recorded depending upon the clinical judgment of the anesthetist as he appraised the patient in the operating room.

Approximately 90% of the patients included in the study were observed the night prior to operation by the anesthetist who was to administer the anesthetic. Eighty-two per cent of the patients were service patients, and the remainder semiprivate or private. Seventy-five per cent were women. The age distribution is indicated in figure 1.

TABLE 1.—*Quantity of Medication Administered According to Patient's Age*

Dose, Ml.	% of Entire Study	% of Patients	
		Aged 60-65	Over 67
0.5	0	0	2
1.0	11	38	53
1.5	36	34	23
2.0	53	28	22

Fifty-three per cent of the patients received 2 ml. of the blind medicament; 36%, 1.5 ml.; and 11%, 1.0 ml. of solution. Table 1 indicates that reasonable clinical judgment was exercised in determining dosage at least on an age basis. However, fewer patients received 2-ml. doses of morphine and alphaprodine as compared to the other three groups (table 2).

Immediate Preanesthetic Period

Mental Status.—The effectiveness of the four drugs and placebo as preanesthetic sedatives on the mental status of the patients is listed in table 3. Of interest is the fact that, when patients were not given sedatives or narcotics, only 36% appeared apprehensive upon arriving in the operating room. Secobarbital reduced this incidence to 21%, which was statistically significant as determined by the chi square test ($p<0.01$). The three narcotics also reduced the number of patients who were apprehensive, but the change was not statistically significant. In this study, therefore, secobarbital proved superior to narcotics in relieving preoperative apprehension. A carefree attitude or one of indifference to the impending operation might be considered as the counterpart of apprehension. Nine per cent of patients to whom a placebo had been administered demonstrated this attitude. Narcotics did not increase the incidence, whereas secobarbital caused indifference in 21% of patients. This was a highly significant change ($p<0.01$).

TABLE 2.—*Quantity of Medication Administered According to Drug**

Dose, Ml.	Saline Solution	Secobarbital	Morphine	Meperidine	Alphaprodine
1.0	8	10	10	11	15
1.5	31	31	45	33	41
2.0	61	59	45	56	44

*Figures expressed as percentages, except dose.

Sedation.—Since sedation is one of the principal reasons for giving preanesthetic drugs, we have analyzed the effectiveness of the drugs in producing a state of drowsiness or in causing the patient to sleep (table 3). Nearly 21% of the patients to whom

a placebo was given either appeared to be drowsy or were observed to be asleep. Both secobarbital and the narcotics increased this incidence significantly ($p<0.01$). The narcotics as a group were significantly superior ($p<0.01$) to secobarbital in this regard. Of interest, however, is the fact that

TABLE 3.—*Preanesthetic Mental Status and Sedation**

	Saline Solution	Secobarbital	Morphine	Meperidine	Alphaprodine
No. of patients	320	192	306	282	303
Apprehensive	36	21	29.5	30.5	33
Carefree	9	21	9.5	19.5	8
Alert	66.5	62	50.5	43	40
Drowsy	19.5	35	37	42	45
Sleeping	1.4	4	5.5	8.5	7

*Figures expressed in percentages, except number of patients.

many patients to whom narcotics had been given and who appeared drowsy were obviously apprehensive nonetheless.

Effect on Blood Pressure, Pulse Rate, and Respiratory Rate.—The influence of the four drugs and the saline solution on blood pressure, pulse rate, and respiratory rate was determined by comparing data obtained on the ward with those recorded in the anesthesia room (table 4). There was no significant difference between the drugs so far as effect upon blood pressure was concerned. However, the narcotics led to an increase in pulse rate more often than did the saline solution or secobarbital ($p<0.01$). This was especially notable when meperidine had been given for premedication. Forty-five per cent of the patients receiving this narcotic had an increase in pulse rate. Because of their well-documented respiratory depressant effect, one might suspect that the narcotics would have a more pronounced influence upon respiratory rate. This was substantiated. Although a lowered respiratory rate was observed less often with saline solu-

TABLE 4.—*Influence of Preanesthetic Medication upon Blood Pressure, Pulse Rate, and Respiratory Rate**

Blood pressure	Saline Solution	Secobarbital	Morphine	Meperidine	Alphaprodine
Unchanged	60	62	55	54	57
Increased	20	17	24	28	25
Decreased	20	21	21	17	18
Pulse rate					
Unchanged	48	54	39	39	47
Increased	31	27	35	45	38
Decreased	21	19	26	16	15
Respiratory rate					
Unchanged	64	67	57	57	54
Increased	13	16	13	13	14
Decreased	23	17	30	29	31

*Figures expressed as percentages. Increase or decrease = 10% or greater change from data observed on ward.

tion as compared with narcotic, the difference was not significant, but that between narcotic and secobarbital was highly significant ($p<0.01$).

Since a 10% change in blood pressure, pulse rate, or respiratory rate may not be meaningful in all cases, an attempt was made to designate those situations in which the changes were of sufficient degree to cause concern to the anesthetist. For instance, concern might be expressed if the pulse rate was increased to 120 per minute, or if the tidal and minute volume of respiration was obviously below normal. The incidence of such occurrences, along with nausea and vomiting and dizziness, is listed in table 5. It is apparent that narcotics led to more problems than did saline solution or secobarbital. The difference in incidence of these sequelae is highly significant ($p<0.01$). It is of interest that nalorphine was required to combat respiratory depression in five patients, one of whom subsequently was shown to have received meperidine, another morphine, and three alphaprodine. When the nalorphine was given, the anesthetist did not know the patient had been given a narcotic, but all five patients responded promptly with an increase in respiratory rate and minute volume.

It was necessary to cancel the operation for two patients, one of whom had been given morphine and developed marked hypotension; the other had

TABLE 5.—*Undesirable Side-effects of Preanesthetic Medication**

	Saline Solution	Secobarbital	Morphine	Meperidine	Alphaprodine
None	88	91	81	70	73
Respiratory depression	4.5	5.2	10†	18†	19†
Hypotension	2.3	2.0	2.3‡	2.1	3
Tachycardia	2.5	0.5	4	4‡	2
Dizziness	3	5	8	11	10
Nausea and/or vomiting	3	1.5	2.3	6.3	2.7

* Figures expressed as percentages.
† Nalorphine required in one case with morphine, one with meperidine, and three with alphaprodine.
‡ Operation canceled for one patient.

been given meperidine and was noted to have a persistent tachycardia of 140 and above. Both patients were rescheduled, at which time atropine alone was given for preanesthetic medication, and in both patients the administration of the anesthesia and the operation proceeded without incident. There were no cancellations of operation for patients receiving saline solution or secobarbital.

Side-effects.—Dizziness was a common side-effect of preanesthetic medication. Patients complained of this even though lying supine on a litter, but most often the complaint came with the movement from litter to operating table. Three per cent of the patients to whom saline solution had been given spoke of dizziness, whereas 5% of those given secobarbital experienced the sensation (table 5). Morphine led to dizziness in 8%, meperidine in 11%, and alphaprodine in 10%. The difference between the narcotics and saline solution was highly significant statistically ($p<0.01$). Nausea and vomiting prior to anesthetization is a well-documented side-effect of narcotics, the incidence of which is related among other things to body position and

motion.[2] In this study, wherein patients remained for the most part in the supine position, there was no significant difference between saline solution and the other drugs. However, the incidence after meperidine was four times higher than that after secobarbital (table 5).

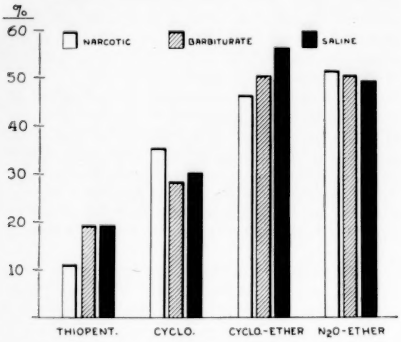

Fig. 2.—Unsatisfactory inductions to anesthesia.

Course of General Anesthesia

In an effort to obtain information on the influence of preanesthetic drugs upon the course of general anesthesia, the anesthetic records of the patients in this study were analyzed as follows:

Induction.—Anesthesia was induced by either thiopental, nitrous oxide, or cyclopropane in the majority of the patients. When thiopental was given, it was usually followed by the inhalation of nitrous oxide or, less commonly, by cyclopropane. Six hundred of the 932 patients under general anesthesia summarized in figure 2 were without the use of thiopental for induction. On the basis of the incidence of satisfactory induction of anesthesia, it is apparent that the individual preanesthetic drug used made little difference. In this clinic, a satisfactory induction to general anesthesia is one without coughing, vomiting, struggling, laryngospasm, excessive respiratory tract secretions, or unintentional apnea.

Preanesthetic medication did, however, influence the type of complication encountered during the induction of anesthesia (fig. 3). If thiopental was injected to induce anesthesia and secobarbital was the preanesthetic sedative, coughing and laryngospasm were the common complications. When the placebo had been given, unusually large amounts of thiopental were required for induction. When anesthesia was induced with cyclopropane, the incidence of unsatisfactory inductions was higher than with thiopental. Where narcotics had been given for preanesthetic medication, excitement and unintentional apnea were more common than when secobarbital or a placebo had been used. The principal problems occurring with cyclopropane after secobarbital sedation were coughing, laryngospasm, and respiratory obstruction. The addition of ether to cyclopropane increased the incidence of complications. Coughing and excessive respiratory tract secretions were common after secobarbital premedication, whereas unintentional apnea appeared frequently after narcotics had been given. When the nitrous oxide–ether sequence was used, little difference was noted in the incidence of induction complications after secobarbital, placebo, or narcotic, except that slowness of induction was often observed after secobarbital. Apnea was notably uncommon after any medication with this sequence.

Maintenance.—Analysis of the influence of preanesthetic medication upon anesthetic complications occurring during maintenance of general or spinal anesthesia proved to be difficult because of the large number of factors involved. Attempts were made to analyze the effect of medication upon the incidence of hypotension, hypertension, bradycardia, tachycardia, respiratory depression, tachypnea, coughing and laryngospasm, excessive secretions, and excessive anesthetic agent. No significant difference could be detected when patients receiving narcotics were compared with those given barbiturates in any of these functions except that respiratory depression was noted three times more often with the narcotics. When trifluoroethyl vinyl ether (Fluoromar) was the principal anesthetic agent, tachypnea was common if barbiturates were given and less common if narcotics had been administered.[3]

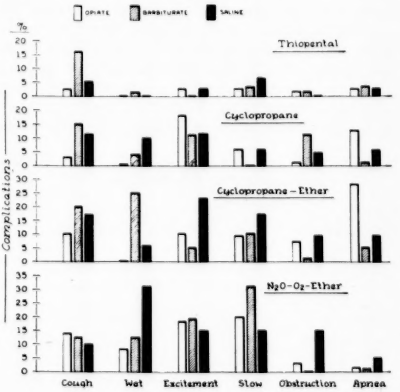

Fig. 3—Incidence of complications with preanesthetic medication during induction to anesthesia.

Recovery.—A comparison of the recovery phase of anesthesia in patients receiving the various preanesthetic drugs was also difficult because of the number of variables. No apparent difference was seen in the incidence of immediate postoperative vomiting or hypotension. However, obvious differences could be discerned in the rapidity of recovery from general anesthesia, in the incidence of postoperative restlessness and excitement, and in complaints of pain in the recovery room.

Rapidity of recovery according to the preanesthetic drugs is recorded in figure 4. This was determined by clinical examination. If a patient was awake upon arrival in the recovery room, his awakening was judged to be rapid. If he was still asleep one hour after arriving there, his recovery was considered prolonged. It is apparent that patients receiving narcotics slept longer than those given secobarbital or saline solution.

Emergence restlessness or excitement was recorded if the patient tossed and turned on his litter

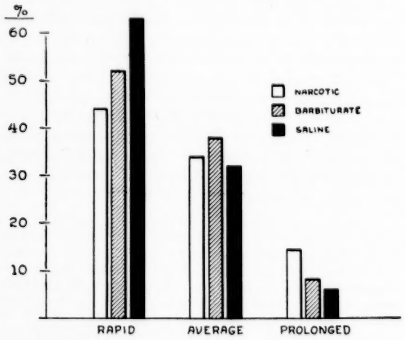

Fig. 4—Rapidity of recovery from general anesthesia according to preanesthetic medication.

or bed, was restless or behaved in a disoriented fashion, or required unusual restraint to prevent falling from the litter. Complaints of pain were not considered restlessness. Figure 5 depicts the incidence of restlessness and excitement according to the anesthetic agents and preanesthetic medication. It is evident that the incidence was highest with saline solution or barbiturate for each of the anesthetics or combination of anesthetics.

Fewer patients complained of pain in the recovery room when they had received narcotics for anesthetic medication (14%) than did those given barbiturate (19%) or saline solution (20%). It is interesting that when saline solution had been given only one in five patients complained of immediate postoperative pain. An analysis of the duration of operation in these patients revealed that those who had opiates and complained of pain had operations averaging three hours, those with saline solution averaged three hours and six minutes, and those with barbiturate averaged two hours and three minutes.

Recognition by Anesthetist of Type of Preanesthetic Medication Given.—Cohen and Beecher [1] re-

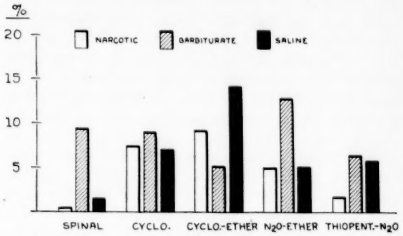

Fig. 5—Incidence of excitement on emergence according to anesthetic agents and preanesthetic medication.

ported that anesthetists were unable to determine by observation what preanesthetic drugs had been given. We have likewise asked anesthetists to indicate their guess as to the nature of the medicament given. The results are in table 6. In this study, the anesthetists' guesses were reasonably accurate, except when secobarbital had been given.

Comment

In the early days of anesthesia the induction of anesthesia with ether or with chloroform in a healthy, robust individual was often a harrowing experience to patient and his anesthetist as well. Concern was expressed frequently over prolonged excitement and the large amounts of anesthetic required to keep patients asleep for long operations. The first recorded uses of morphine to supplement general anesthetics appeared as a solution to these problems.[4]

Today the use of preanesthetic medication is primarily to produce sedation.[4A] Preanesthetic narcotics may be given to relieve pain, but most patients scheduled for operation are not in pain. The degree of sedation desirable prior to anesthesia

TABLE 6.—*Anesthetist's Guess as to Preanesthetic Medicament**

	Saline Solution	Secobarbital	Morphine	Meperidine	Alphaprodine
Narcotic	19	29	63	83	67
Nonopiate ..	19	32	19	15	18
Placebo	62	39	18	2	15

* Percentage of guesses correct.

and operation is debatable. Many believe an ideal state to exist when the patient is sleeping but rousable, and when there is retrograde amnesia for the anesthetic and operative experience. If this state could be produced without harm to the pa-

tient, there would be little ground for argument. If the hazard is significant, search must be made for drugs with less drawbacks. Lacking such agents, a compromise must be made in the desirable preoperative condition of the patient.

There can be no question that the narcotics are unequaled as analgesics. There is likewise agreement that the narcotics have many undesirable side-effects.[5] The data presented show that the incidence of undesirable side-reactions to the narcotics studied are considerable and are greater than those observed after secobarbital. They also demonstrate the superiority of narcotics over secobarbital in producing drowsiness or sleep in pain-free patients. However, this was associated with a higher incidence of apprehension and concern for the approaching operation than noted with the barbiturate. Of especial note is the fact that without sedatives or narcotics, 64% of patients evinced no preoperative apprehension. Secobarbital raised this to 79%. The routine use of narcotics for preoperative medication, therefore, exposes all patients to the hazards of these drugs in an attempt to obtain sedation in 20% of surgical patients.

Do preanesthetic narcotics reduce the incidence of excitement during induction of anesthesia? Cohen and Beecher [1] concluded that "when utilizing a given anesthetic agent, there is little difference in response to the various drugs used for preanesthetic medication. The patient's response to the various anesthetic agents, however, did vary." Our experience supports this view (fig. 2 and 3). It may be of significance that, when narcotics were administered preoperatively, respiratory tract secretions were a minor problem with all combinations of anesthetic agents during induction, whereas excessive secretions were a common complication with saline solution or secobarbital. It would appear that the dose of belladonna should be increased if it is to be given alone or in combination with a barbiturate.

How does one reconcile the fact that preanesthetic narcotics were apparently originally used to diminish the incidence and severity of excitement during induction of anesthesia and that neither Cohen and Beecher nor ourselves have been able to substantiate this? Preanesthetic medication was introduced at the time when chloroform and ether were the only commonly used anesthetic agents. The nitrous oxide–ether sequence had not been described. Both chloroform and ether have a high air:blood partition coefficient. Therefore, they must be present in high concentration for surgical anesthesia. As this level is slowly developed, a prolonged excitement stage is encountered. Morphine minimized excitement by producing sedation and apparently by augmenting the anesthetic. The hazard of narcotic plus anesthetic appeared less than that of a prolonged stormy induction and high anesthetic concentration. Today, however, intravenously administered barbiturates usually permit rapid and pleasant induction, and general anesthetic agents are available which have a low partition coefficient, and therefore a shorter induction period. When diethyl ether is to be used, induction of anesthesia is possible with nitrous oxide, ethylene, cyclopropane, vinyl ether, or ethyl chloride. Because of the rapidity of action of these agents, the need for additional depressants has been minimized. If our studies had been conducted upon patients to whom ether or chloroform was to be given for induction as well as maintenance, our results might have been different.

We did not obtain data in this study as to whether or not narcotics decrease the concentration of anesthetic needed to maintain a given plane of anesthesia. In another study,[6] we have advanced evidence to suggest that inhalant anesthetics may alter cell permeability or cell response, so that the effect of a given blood-stream concentration of nonvolatile central nervous system depressant is intensified. The observation that apnea occurred frequently when narcotics were given prior to cyclopropane or cyclopropane–ether anesthesia supports this thesis. If narcotics allowed for a lesser concentration of anesthetic, one would still have to balance the advantage of a slightly diminished concentration of inhalant anesthetic versus the hazards of the opiate. It is of interest to note that, in 1890, Horatio Wood [7] expressed an opinion on this subject when he wrote

> A-priori reasoning would render it probable that anesthesia would be more easily produced and would be more prolonged in the semi-narcotized patient than in the normal individual, and clinical experience has confirmed this. But in the prolongation of anesthesia would seem to lurk a danger. Certainly, it is but natural to suppose that an anesthetic accident occurring in a person who is under the influence not only of a volatile and easily dissipated poison, but also of a non-volatile and comparatively permanent poison would be far more serious than if the failure of respiration and of circulation were the outcome of an agent which could rapidly be removed. Several surgeons have shown that this reasoning is not devoid of practical support and a number of cases have been published in which very serious symptoms, or even death, have occurred during the mixed narcotism.

In view of the line of reasoning taken by Wood, secobarbital offers a certain advantage over the narcotics in its brevity of action. Narcotics continue to exert an influence for many hours,[5] whereas the barbiturate injected intramuscularly dissipates its effect in about two hours. This is an advantage should difficulty arise.

Patients who have had narcotics take longer to recover from anesthesia (fig. 4), an observation that agrees with those of early investigators.[4b] There are advantages of early awakening, such as more rapid return of protective reflexes with less hazard of respiratory obstruction or aspiration of vomitus and the need for less close postanesthetic super-

vision. These are important considerations in the absence of recovery rooms or where nursing personnel is at a premium. There are also disadvantages to rapid awakening, such as the earlier perception of pain and greater discomfort for the patient in the immediate postanesthetic period (fig. 5). Restlessness and complaints of pain were more common in patients given barbiturates or saline solution.[8] However, only one patient in five who received saline solution complained of pain in the recovery room, whereas one of seven who had had narcotic complained of pain.

What are some of the criteria by which an anesthetist chooses preanesthetic sedatives or narcotics? One of the more obvious is the age and physical status of the patient. Elderly, sedentary, and chronically or acutely ill patients should receive narcotics uncommonly. One need be less concerned about the healthy and robust because of their wide margin of tolerance. Excitable, nervous, and apprehensive patients require more sedation than do those who are calm and philosophical. In this regard, the anesthetist should never underestimate the value of the preanesthetic visit and discussion with the patient. The establishment of rapport and confidence will do more to allay fears and produce calmness than any amount of narcotics or barbiturates, and it is far safer for the patient.

A second criterion is the anesthetic technique the anesthetist will use. If potent general anesthetics such as cyclopropane or ether are contemplated, narcotics are not necessary. If a less potent combination such as an intravenously administered barbiturate and nitrous oxide is planned, narcotics are also unnecessary if the proposed operation will not be associated with great pain, nor relaxation be needed. However, in extensive operations associated with considerable dissection and need for relaxation, narcotics will probably be needed.

Surgeons often unwittingly commit the anesthetist to drugs and procedures that are not in the best interest of the patient. Thus promises are made that a patient will be oblivious of his trip to the operating room or that he will have no pain postoperatively. A surgeon may insist unnecessarily upon the use of the electrocautery during an operation. The latter forces the anesthetist to use a nonexplosive technique usually calling for increased narcotic preanesthetic medication or supplementation of a thiopental–nitrous oxide relaxant anesthesia with narcotics given intravenously. The dangers of this combination in certain patients may outweigh any possible advantages of reduced blood loss or operating time.

Each patient must be considered individually and each anesthetic and operation must be viewed objectively. Preoperative medication should be tailored to meet the needs of the patient and his operation. With the anesthetic agents and techniques available today, there is no place for "routine preanesthetic medication." Our continued study of this problem has led us to believe that the optimum condition of patients brought to the operating room is awake and alert, yet free of apprehension. It is safest this way. The data presented suggest that the continued routine use of narcotics for preanesthetic medication is unwise and unwarranted. We do not advocate abandoning preanesthetic use of narcotics, but we do believe they should only be ordered with a specific objective in mind and with an awareness of the hazards inherent in their use.

Summary

Data obtained in a blind study of morphine, meperidine, alphaprodine, secobarbital, and saline solution as preanesthetic medicaments in 1,400 surgical patients showed that secobarbital led to a higher proportion of calm, carefree, yet alert patients than did the narcotics. The latter drugs produced more drowsy or sleeping patients but also a higher incidence of apprehension than did secobarbital. Undesirable side-effects were seen more often after preanesthetic narcotics than with secobarbital. There was little difference in the influence of the various preanesthetic drugs upon satisfactory induction of anesthesia with any given anesthetic agent. However, the complications of the induction period did vary according to the preanesthetic drug and the anesthetic agent.

Preanesthetic drugs did not appear to influence the maintenance of anesthesia, except that respiratory depression was more common if a preanesthetic narcotic had been given. When narcotics had been given preoperatively, the patient remained narcotized longer after anesthesia than did those who received secobarbital or saline solution, but they did not complain of pain as often nor appear as restless as did the latter groups. These data are significant in the clinical practice of anesthesia.

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The alphaprodine used in this study was supplied as Nisentil by Hoffman-La Roche, Inc., Nutley, N. J., who also supplied the morphine. The secobarbital was supplied as Seconal by Eli Lilly & Company, Indianapolis.

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SIGNIFICANCE OF FATAL PULMONARY EMBOLISM IN IMMEDIATE POSTOPERATIVE PERIOD

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Factors that might predispose a patient to fatal postoperative pulmonary embolism were sought in a study of 943 autopsy records representing 10 years of hospital experience. Pulmonary embolism was demonstrated in 118 cases and considered to be the primary cause of death in 49. In 22 cases fatal pulmonary embolism followed a major operation. Four of these 22 deaths occurred during the first 24-hour period after surgery. Fever and tachycardia were present preoperatively in five of six patients who died within the first 72 hours after operation. Almost one-half of the postoperative group were limited in physical activity prior to surgery. These findings suggest that an underlying thrombotic process may have been present at the time of operation. Thus, preventive measures routinely employed after surgery would appear to be equally important during the preoperative period.

Fatal pulmonary embolism continues to threaten the convalescence of both medical and surgical patients. Few subjects have prompted more intensive investigation, yet little encouragement is provided by statistical studies, which show a rather constant incidence over the past 50 years.[1] Certainly, progress has been made in the management of thromboembolism, and especially in the treatment of acute phlebitis and its complications. Unfortunately, however, fatal pulmonary embolism frequently originates from an asymptomatic extremity, and its occurrence is the first manifestation of an underlying phlebothrombosis.

Because of the problems encountered in diagnosis of phlebothrombosis and the lack of a satisfactory treatment once massive embolism has occurred, attention is directed toward the prevention of thrombosis. Predisposing factors, including advanced age, limitation of activity, obesity, hypoproteinemia, anemia, dehydration, and the presence of cancer, have been implicated. Although correction of such abnormalities is recognized as extremely important, it is not always obtainable, and to date preventive measures have not eliminated sudden unexpected fatal pulmonary embolism in the postsurgical patient.

The recent occurrence of four cases of fatal pulmonary embolism in the immediate postoperative period stimulated our interest in the problem. Not only did it appear worthwhile to investigate this relatively unusual event and its significance in the entire problem of postoperative thromboembolism, but also it provided an opportunity to review the general subject of pulmonary embolism at Passavant Memorial Hospital for the past 10-year period.

A total of 943 autopsies of adults were performed between July 1, 1947, and June 30, 1957, and pulmonary embolism was demonstrated in 118 instances (12.5%). In 49 patients (5.2%) embolism was considered to be the primary cause of death, and of this group 22 died after an operation. During the same period, 26,688 major surgical procedures were performed; this gives a postoperative

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incidence of 0.082%. The remaining 27 deaths directly attributable to pulmonary embolism occurred either in patients on the medical services or in patients with surgical problems treated by nonoperative measures. In 69 patients the embolism was associated with another, more significant cause of death.

Fatal Postoperative Embolism

In the 22 cases of postoperative fatal pulmonary embolism reviewed, the ages of the patients ranged from 26 to 81, with an average of 55 years. There were 12 females and 10 males. The primary disease, as well as the type of surgical therapy and associated complicating factors, are tabulated in the table. Nine patients died after neurosurgical procedures, six after colon surgery, and three after gynecologic operations. Also, fatal embolism followed a jejunostomy and splenectomy, an esophagogastrectomy, an open reduction of a fracture, and a thyroidectomy. One-half of the patients suffered from some form of cancer. In 15 instances the postoperative course was complicated. Four patients developed postoperative infections and seven were limited in activity as a result of either hemiparesis or a semicomatose or comatose state. A wound disruption, a postoperative abdominal hemorrhage, and a decubitus ulcer accounted for three complications. In the remaining patient, though no specific complication could be defined, the postoperative course was stormy, with recurrent bouts of nausea, vomiting, and weakness, which limited ambulation. Only seven patients appeared to be recovering in a normal manner.

Activity preceding surgery was considered good in only 12 patients. The remainder were limited either because of their illness or the restrictions of hospitalization. Activity after operation was considered adequate when the patient was ambulatory by the third postoperative day; prior to this time, care was taken to encourage deep breathing as well as active and passive exercises of the lower extremities. Only six patients achieved these criteria; the remainder were limited to lesser degrees of activity.

Twelve patients had intravenous infusions during or after operation in one or both lower extremities, and seven developed evidence of phlebitis in the leg used for infusion. Embolism was preceded by phlebitis in a total of 10 patients. It is important to note that in over one-half of the group fatal embolism was the first evidence of thromboembolic disease.

Low-grade elevations in temperature (99 to 100 F [37.2 to 37.8 C]) and pulse (80 to 100 beats per minute) were noted preoperatively in 12 instances. Similar findings were observed in all but one patient after operation. In five of six patients who died within the first 72 hours, low-grade fever and tachycardia were present prior to surgery.

The symptoms and physical findings associated with fatal pulmonary embolism, in order of frequency, were as follows: tachycardia in 22 patients, cyanosis in 16, dyspnea in 14, tachypnea in 9, diaphoresis in 5, hypotension in 5, cough in 2, rales in 2, hemoptysis in 1, and pain in 1. Thus we see that, in addition to the expected tachycardia and either tachypnea or dyspnea, cyanosis was a remarkably frequent finding. Diaphoresis and hypotension were noted less often, while cough, hemoptysis, rales, and pain occurred only occasionally.

Data on Fatal Postoperative Pulmonary Embolism in Twenty-two Patients

Case No.	Primary Disease	Operation	Complications
1	Leiomyoma, esophagus	Esophagectomy with esophagogastrostomy	Peritonitis, empyema
2	Uterine fibromas	Complete abdominal hysterectomy	None
3	Ruptured ovarian cyst	Salpingo-oophorectomy	Reoperation for intra-abdominal bleeding
4	Recurrent cystourethrocele; functional uterine bleeding	Complete abdominal hysterectomy; repair cysto-urethrocele	None
5	Astrocytoma	Craniotomy	None
6	Carcinoma (sigmoid)	Sigmoid resection, colostomy, distal stump left in situ	Pelvic abscess
7	Carcinoma (esophagus)	Jejunostomy, splenectomy	Wound dehiscence
8	Fracture (patella)	Open reduction, wire fixation (patella)	None
9	Carcinoma (rectosigmoid) with perforation and peritonitis; periappendiceal abscess	Drainage (periappendiceal abscess)	Peritonitis
10	Meningioma	Craniotomy	Coma
11	Glioblastoma multiforme	Craniotomy	Decubitus
12	Trigeminal neuralgia	Trigeminal neurectomy	Coma
13	Perforated sigmoid diverticulitis	Transverse colostomy	Intestinal obstruction, peritonitis
14	Recurrent astrocytoma	Craniotomy	Hemiparesis
15	Glioblastoma multiforme	Craniotomy	Hemiparesis
16	Meningioma	Craniotomy	Coma
17	Carcinoma (ascending colon)	Right hemicolectomy	None
18	Astroblastoma	Craniotomy	Pneumonia, stupor
19	Suspect intracranial tumor	Craniotomy	Hemiparesis, coma
20	Thyroid cyst (substernal)	Thyroidectomy	None
21	Carcinoma (prostate) with widespread disease	Sigmoid colostomy	None
22	Carcinoma (sigmoid)	Abdominoperineal resection	Poor response postoperatively

The time interval between operation and the onset of fatal pulmonary embolism varied from 4½ hours to 60 days. The average time was 19 days. Seven patients developed a fatal embolism before the seventh postoperative day, while 4 embolisms occurred during the second week and 11 in the period that followed.

The exact survival from onset of symptoms until death is difficult to define. Several patients had severe respiratory distress for considerable periods of time prior to death, while others died almost instantaneously. Twelve patients died within the

first hour of symptoms. The remainder lived for intervals of 1 hour to 11 days after the initial symptoms attributable to embolism became apparent.

Fatal Pulmonary Embolism in Immediate Postoperative Period

Four patients died as a result of pulmonary embolism in the first 24 hours following a major surgical procedure. This is a relatively infrequent event, though isolated instances have been reported.[2] A brief clinical summary of each case follows.

Report of Cases

CASE 1.—An 80-year-old female was hospitalized on June 16, 1956, for evaluation of an episode of rectal bleeding. The remainder of the history was negative, except for pernicious anemia, which was controlled by medical management. Physical examination was unremarkable, except for mild hypertension and the presence of gross blood on rectal examination. Laboratory studies revealed an admission hemoglobin level of 8.8 Gm. per 100 cc., a hematocrit of 28%, and a sedimentation rate of 15 mm. per hour (Wintrobe). A barium enema demonstrated an annular lesion in the ascending colon.

During the 14-day period of hospitalization before operation, daily low-grade elevations of temperature (99.4 to 100 F [37.4 to 37.8 C]) and pulse (80 to 90) were noted, except during the last four days prior to surgery, when the temperature was normal. Her activity was limited during the entire preoperative period.

After adequate preparation a hemicolectomy was performed on June 30, 1956, to remove an adenocarcinoma of the ascending colon. Except for a short period of hypotension which occurred initially, the operative procedure was uneventful. The operation was completed in less than three hours, and in the immediate postoperative period the patient responded well. Three hours after surgery, the blood pressure was 160/90 mm. Hg, the pulse rate was 88, and she was conscious. Five hours after the operation she developed severe diaphoresis and within 15 minutes became dyspneic and cyanotic. Symptomatic treatment was given without benefit, and she died 6 hours and 45 minutes after completion of the procedure.

Autopsy revealed an embolus lodged in the main pulmonary artery and extending into the left branch. The lungs were hyperemic and congested. Due to the size of the embolus the source was believed to be one of the large veins of the lower extremities.

The combination of advanced age and cancer plus the restriction of normal activity imposed by hospitalization were strong predisposing factors for thrombus formation. The preoperative low-grade fever and tachycardia were interpreted as resulting from infection in and around the tumor but may have originated, at least in part, from a low-grade phlebitic process. The hypotension at the time of operation, though of short duration, may have contributed to the formation of a fresh propagating thrombus.

CASE 2.—A 65-year-old female was hospitalized on Dec. 16, 1956, for evaluation and treatment of a cervical mass that produced symptoms of pressure in the throat and difficulty in breathing. The patient had also noticed a change in voice during the preceding six months. Physical examination was normal, except for a palpable left cervical mass, which moved on swallowing. Laboratory studies were within normal limits. Roentgenograms of the chest revealed deviation of the trachea to the right and, in addition, an area of increased density in the middle lobe. After appropriate studies and institution of therapy, the patient was discharged. She was readmitted on Dec. 26, 1956, at which time chest x-rays showed disappearance of the middle lobe density. During the preoperative hospital stay, activity was curtailed below normal, and on several occasions a low-grade fever was noted.

On Jan. 3, 1957, bronchoscopy under general anesthesia revealed normal vocal cords and tracheobronchial tree. On completion of bronchoscopy, a left thyroid lobectomy was performed without difficulty. Postoperatively she responded well, and the vital signs were stable. Four hours and 20 minutes after completion of the operation she suddenly died without cyanosis or other respiratory distress preceding.

Autopsy revealed an antemortem clot straddling the bifurcation of the left and right pulmonary arteries. The lungs were edematous and hyperemic. The ovarian veins contained thrombi, and the iliac veins were patent; however, the size and length of the thrombus indicated origination from a large leg vein.

Here, again, an older individual was restricted to a level of activity below normal prior to surgery. The low-grade fever may have originated from the thrombotic process, which eventually proved fatal.

CASE 3.—A 66-year-old male was hospitalized on March 10, 1957, in a confused state, with a history of hematuria, fecal incontinence, and melena for a period of one month. Examination at the time of admission revealed abdominal distention, with multiple hard masses in the right upper quadrant, epigastrium, and left lower quadrant. The admission diagnosis was probable carcinoma of the colon, with invasion of the bladder, and abdominal carcinomatosis. Laboratory studies were normal, except for the findings of 15 to 30 white blood cells in the urine and 1+ albuminuria. The hemoglobin level was 14.3 Gm. per 100 cc., hematocrit 44%, and sedimentation rate 19 mm. per hour.

For the week preceding operation there was a low-grade elevation of temperature (99.6 F [37.6 C]) and pulse (80 to 96 beats per minute) each day. Because of the degree of debility and confusion, activity was extremely limited preoperatively.

On March 18, 1957, a colostomy was performed to relieve a colonic obstruction. Exploration revealed abdominal carcinomatosis, which included large masses in the liver and urinary bladder. During the operation 500 cc. of whole blood was given, and the blood pressure was stable throughout. Nineteen hours after completion of the operation the patient suddenly became cyanotic, with profuse diaphoresis and hypotension. Despite symptomatic treatment he died.

Autopsy demonstrated the primary tumor to originate from the prostate. There was an embolus straddling the pulmonary artery bifurcation, and the lungs were congested and hyperemic. There were metastatic nodules over the pleural surfaces of both lungs. Here, again, the size of the embolus suggested the large veins of the legs as the source.

Age, presence of carcinomatosis, and restriction of activity all predisposed this patient to thrombosis and later to the massive embolism. The fever and tachycardia suggest a low-grade inflammatory process, such as phlebitis.

CASE 4.—A 46-year-old male was hospitalized on March 15, 1954, for treatment of a trigeminal neuralgia on the right, which began 18 months prior to admission. History, physical examination, and routine laboratory studies were normal except for a mild hypertension (166/96 mm. Hg).

On March 17, 1954, trigeminal neurectomy was attempted but was discontinued when the blood pressure fell precipitously. During the hypotensive episode, the patient be-

came unresponsive. The blood pressure stabilized rapidly and remained stable during the immediate postoperative period.

During the first 24 hours after surgery he remained unresponsive but thereafter began to improve rapidly. Electrocardiograms revealed no diagnostic abnormality. During the next 10 days activity was limited by a residual weakness of the left side. After surgery there was a low-grade fever (99 to 100 F [37.2 to 37.8 C]) and tachycardia (80 to 90 beats per minute) for three days, after which he was afebrile. Serial electrocardiograms revealed no change during this period.

The patient continued to experience severe facial pain, and for this reason a right trigeminal neurectomy was carried out, with the patient under local anesthesia, on March 29, 1954. On completion of the procedure he was alert, and vital signs remained stable.

One hour after returning to his room he again became unresponsive, and marked rigidity was noted over the right side of the body. His blood pressure was 120/80 mm. Hg, and slight cynanosis was noted. Improvement followed administration of oxygen and tracheal aspiration. Six hours after surgery he appeared more responsive, and the rigidity disappeared. Deep tendon reflexes were equal bilaterally. The blood pressure was stabilized at 150/90 mm. Hg, and the cyanosis had disappeared.

He died suddenly 13 hours after completion of the procedure. Immediately preceding death there had been no significant change in findings.

Autopsy revealed an antemortem clot occluding the left pulmonary artery, and the left lung was filled with blood. An additional finding was a recent area of myocardial infarction localized in the interventricular septum. An incidental finding was a small carcinoma of the prostate.

The limitation of activity following the first operation may well have been a predisposing factor to thrombus formation. The transient hypotension during the first procedure probably coincided with the myocardial infarction; however, rapid stabilization of vital signs and the lack of electrocardiographic changes gave little reason to suspect this clinically.

Comment

Pulmonary embolism was demonstrated in 118 (12.5%) of 943 autopsies of adults, and embolism was considered to be directly responsible for death in 5.2% of the cases. McCartney [3] found an incidence of embolism of 10% in 25,771 autopsies; however, fatal embolism accounted for only 2.67% of the deaths. This compares closely with the collective study of Bailey,[1b] who found the incidence of fatal embolism in 80,802 autopsies to be 2.6%. The disparity between our results and those of others probably arises from the difference in size of the series studied.

Of 118 cases of pulmonary embolism reviewed, 96 occurred either in medical patients or in surgical patients in whom no operation was performed. Twenty-seven deaths in this group were considered directly attributable to the embolism. In 17 instances embolism was associated with cardiovascular disease. Nine patients had some form of cancer, and in one patient debility followed a severe rheumatoid arthritis. In 69 patients the embolism was considered sublethal; the primary cause of death was cardiovascular disease in 51, cancer in 13, renal disease in 3, and cirrhosis and an undefined anemia in one case each. The importance of pulmonary embolism in medical patients has been emphasized by Carlotti and associates.[4] They observed that more than 50% of all pulmonary emboli occurred on the medical services during a period when there were twice as many surgical as medical admissions. Embolism was associated with heart disease in 66% of these patients.

In this series postoperative fatal pulmonary embolism was proved by autopsy in 22 patients during a period when 26,688 major operations were performed. This incidence (0.082%) is comparable to that found by Wilson [5] (0.08%) but considerably lower than the average of many collected series. Bailey [1b] found an average incidence of 0.23% in 462,381 operations and others have reported similar results.[6] DeBakey [1d] emphasized the importance of an "irregular wave-like periodicity" that produces wide fluctuations of incidence. Another factor that probably contributes to our lower incidence is the inclusion of only those cases proved by autopsy examination. We feel justified in excluding cases in which the diagnosis of fatal embolism was based on clinical impression alone.

It is important to differentiate, in any sudden postoperative cardiopulmonary complication, between myocardial infarction and massive pulmonary embolism, since treatment of the two conditions is considerably different. While tachycardia, dyspnea, diaphoresis, and hypotension may be prominent findings in either instance, cyanosis is not commonly observed in myocardial infarction unless cardiac failure is associated. Sixteen of the 22 patients in this study were cyanotic prior to death. Poltz [7] has also emphasized this important differential point. Chest pain was not common in our series; however, others have described the pain of massive embolism as indistinguishable from that of myocardial infarction.[8]

The relationship in this study between fatal pulmonary embolism and such factors as age, sex, types of operations performed, timing between operation and death, and timing between onset of symptoms and death are in general comparable to those observed by others.[9]

Several factors are worthy of further consideration: 1. Four of the 22 deaths occurred during the first 24-hour period following operation. 2. In almost one-half of the patients activity was restricted prior to operation. 3. Low-grade fever and tachycardia were present preoperatively in five of six patients who died within the first 72 hours after operation.

These findings suggest that an underlying thrombotic process was present at the time of surgery. The possibility that thrombosis may exist in patients referred for surgery after a period of preoperative evaluation or conservative care is an important and often little-considered potentiality.

Hunter [10] found that 50% of patients autopsied who had died after variable periods of confinement to bed had deep vein thrombosis. Of all factors etiologically significant in thromboembolism, no other appears more significant than the limitation of normal activity imposed either by the patient's disease or by the restrictions of hospitalization. Such restriction, though often relative, may result in a reduction of venous flow, which doubtless forms the broad base upon which all thromboembolic phenomena are dependent.

The preoperative evaluation of all surgical candidates should include a careful study of factors that might predispose to potential or actual thrombotic disease, such as advanced age, cancer, obesity, infections, heart disease, dehydration, anemia, or a history of previous thromboembolic disease. A normal level of activity should be resumed prior to any elective surgical procedure. The importance of correcting abnormal physiological states, including anemia and dehydration, and the use of appropriate measures to facilitate venous return from the lower extremities, hardly need be mentioned. The use of intravenous infusions in the lower extremities of patients who may be limited in activity postoperatively should be condemned.

It is our opinion that the inability to control postoperative pulmonary embolism by early ambulation and other therapeutic measures may represent failure to recognize the presence of a thrombotic process preceding the surgical procedure. Indeed, it is possible that some individuals with a low-grade phlebitis before operation may form a fresh, poorly adherent, propagating thrombus during the operation if the venous return from the lower extremities is reduced significantly. In the immediate postoperative period choking, vomiting, straining when recovering from anesthesia, or activities associated with early ambulation may produce sudden changes in venous flow that could readily dislodge a loosely adherent clot and result in a fatal pulmonary embolism. Institution of measures to prevent incipient thrombosis in the preoperative period would then seem to be of equal importance to those routinely recommended during the postoperative period.

Summary

During the past 10-year period pulmonary embolism was demonstrated in 118 of 943 autopsies of adults (12.5%). Fatal pulmonary embolism occurred in 22 patients postoperatively. In the same time interval 26,688 major operations were performed; this resulted in an incidence of 0.082%. Four of the 22 postsurgical patients died during the first 24 hours following operation. In each instance a low-grade fever and tachycardia was associated with reduced levels of physical activity imposed by at least one week of hospitalization before surgery.

The combination of restricted activity, fever, and tachycardia prior to operation and a sudden fatal embolism in the immediate postoperative period strongly suggests the presence of thrombosis prior to the time of surgery. It is difficult to establish with certainty the frequency of thrombosis prior to operations; however, in the case of all patients restricted to levels of activity below normal there should be a high degree of suspicion.

It is possible that many fatal pulmonary emboli originate from a low-grade phlebothrombosis that begins before operation. In those instances preoperative prophylaxis is of equal importance to preventive measures instituted in the postoperative period.

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POLYNEURITIS OCCURRING DURING HYDRALAZINE THERAPY

REPORT OF TWO CASES AND DISCUSSION OF ADVERSE REACTIONS TO HYDRALAZINE

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Areas of soreness and numbness developed in two patients who were being treated for hypertension. In one the pain was especially severe and accompanied by weakness of certain muscles; in both patients the neurological findings were characteristic of polyneuritis. Remission of these symptoms followed promptly after the use of hydralazine as part of the antihypertensive treatment was discontinued. The patients had been receiving 700 and 600 mg. of hydralazine, respectively, per day. These dosages are considered rather high, and the polyneuritic symptoms have occurred only in these two instances among 700 patients treated with hydralazine during a five-year period. A syndrome resembling lupus erythematosus has been seen in six instances. There was evidence that the two patients here discussed were predisposed to polyneuritis by a previous low dietary intake of pyridoxine. It is recommended that polyneuritis occurring under these conditions be treated by discontinuing the hydralazine therapy and administering pyridoxine.

The syndrome resembling lupus erythematosus is a well-known and dramatic complication of hydralazine (Apresoline) hydrochloride therapy.[1] Other potentially troublesome characteristics of hydralazine are not so well known. For example, it is not generally known that hydralazine, like isoniazid, can form a stable chelate with certain trace minerals and that it is an antienzyme for several biological systems.[2] Experience with two patients suggests that hydralazine, like isoniazid, may cause peripheral neuritis, possibly by interference with pyridoxine metabolism. The English-language literature on the subject has been reviewed, and no report of polyneuritis occurring during therapy with this drug has been found. Biehl and Vilter,[3] however, in discussing polyneuritis due to isoniazid, suggested that hydralazine, because of its chemical structure, might also cause certain specific vitamin deficiencies in man.

Report of Cases

CASE 1.—A 62-year-old man was admitted to the Veterans Administration Hospital, Iowa City, on June 1, 1954. One year prior to admission the patient had noted fatigue and exertional dyspnea. Four months prior to admission he developed severe retro-orbital and occipital headaches, nausea, and vomiting. Because of progressive decrease in vision, he consulted an ophthalmologist and was told that his blood pressure was "245" mm. Hg. His vision became more blurred, and he noted swelling of the ankles and hands. These complaints brought him to the hospital.

His medical history was negative. There was no history of diabetes mellitus, and the family history was negative for pertinent disease. For years he had drunk two to three bottles of beer per day, and usually one-fifth gallon of whiskey each week. Physical examination on admission revealed the patient to be a well-developed, well-nourished, florid-faced man. Blood pressure was 250/140 mm. Hg. Funduscopic examination revealed bilateral papilledema, flame-shaped hemorrhages, soft and hard exudates, marked narrowing of the arterioles, considerable arteriovenous nicking, and early distention of the veins. The left border of cardiac dulness was outside the left midclavicular line. There was a grade 1 apical systolic murmur, and the aortic closure sound was accentuated markedly, but there was no evidence of cardiac failure. All peripheral pulses were palpable. Neurological examination showed reflexes to be equal and physiologic on the two sides, and there was no evidence of sensory or motor deficit. His body weight on admission was 152 lb. (68.9 kg.). After the first week of hospitalization, his weight fluctuated between 138 and 144 lb. (62.6 and 65.3 kg.) throughout his stay.

Initial laboratory examinations, including red blood cell count, hemoglobin level, sedimentation rate, serologic test for syphilis, blood urea nitrogen and creatinine levels, plasma carbon dioxide content, and serum chlorides level, were normal. White blood cell count was 12,400 per cubic millimeter, with 74% of the cells mature polymorphonuclear leukocytes. Urinalysis revealed 2+ proteinuria, 70-80 white blood cells, and 11-15 red blood cells per high-power field. No urinary glucose was found on a number of examinations. A test for pheochromocytoma with use of phentolamine was negative. On June 23, 1954, the blood urea nitrogen level was 33 mg.%, and it remained at about this level until Aug. 10, 1954, when it fell to 21 mg.%. After this date, the blood urea nitrogen level was consistently normal. Phenolsulfonphthalein excretion in two hours was 66%. Cephalin flocculation test, total serum protein level, and serum albumin and globulin levels were normal. Several electrocardiograms revealed left ventricular hypertrophy. Four urine cultures revealed no growth. Initial x-ray examination of the chest revealed left ventricular hypertrophy. Intravenous pyelograms showed poor function. Retrograde pyelograms revealed findings compatible with changes due to chronic pyelonephritis. Cultures made from urine of each kidney at this time were negative for bacteria. Gastric analysis was done without the use of histamine, and no free acid was found. A tubeless gastric analysis,[4] however, was positive for free gastric acid, and in December, 1954, a duodenal ulcer, apparently new and active, was demonstrated by upper gastrointestinal x-ray series. Renal function studies performed on Aug. 18, 1954, revealed the glomerular

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filtration rate (with use of inulin) to be 65 ml. per minute per 1.73 sq. m., the renal plasma flow (with use of sodium para-aminohippurate) 260 ml. per minute per 1.73 sq. m., and the filtration fraction 25%.

The patient was treated initially with a 500-mg. sodium diet, subcutaneously given hexamethonium chloride, and orally given hydralazine. The dose of hexamethonium was gradually increased from 5 mg. to 40 mg. two times a day. Hydralazine doses were slowly raised from an initial dose of 10 mg. four times a day to a total daily dose of 700 mg. a day (fig. 1). By the 25th hospital day, the blood pressure

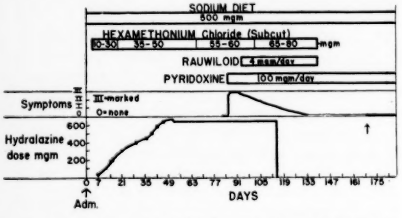

Fig. 1 (case 1).—Relationship between drug administration and symptoms of polyneuritis as estimated from review of chart notes. Total daily dose of hydralazine was 650 mg. from 51st day of hospitalization to 114th day. By 169th day of hospitalization (arrow) all symptoms of polyneuritis had disappeared.

had fallen to 160/110 mm. Hg, and proteinuria, papilledema, and many of the fundic exudates and hemorrhages had disappeared.

On the 83rd hospital day the patient began to complain of soreness and numbness of the right ankle, and five days later soreness and numbness occurred in the same area on the left foot. At this time a clot test for L. E. cells was negative. The area of involvement gradually increased in size until there was a hand-sized area of involvement below and anterior to the external malleoli on both lower extremities. In both areas there was decreased perception of pin prick and cotton, and the patient complained bitterly of numbness and pain. Five days after the symptoms appeared, therapy with 100 mg. of pyridoxine a day by mouth was started. Within two weeks after the institution of the pyridoxine therapy the patient complained less of the numbness and tingling of his feet, and the area of involvement began to decrease in size. Nevertheless, shortly after this, hydralazine was withdrawn because it was thought to be the etiological agent. Seven weeks after onset, the area of numbness had decreased in size until it was found only in a 4-cm. circular area on each foot. Eleven weeks from onset, numbness and all symptoms referable to the neuritis had disappeared (fig. 1). A neurological consultant who examined the patient during the acute phases of the illness agreed with the diagnosis of peripheral neuritis.

Subsequently, the patient was treated with the alseroxylon fraction of Rauwolfia serpentina (Rauwiloid), the alkavervir fraction of Veratrum viride (Veriloid), and hexamethonium. On Oct. 19, 1954, the hexamethonium was withdrawn and therapy with orally given pentolinium tartrate was begun. In December, the patient was allowed frequent therapeutic leaves, and he was finally discharged from the hospital on May 20, 1955. He was seen on a follow-up visit on July 20, 1955, at which time he had no evidence of neuritis. He was doing well on a therapeutic program which included pentolinium and reserpine. Later, the patient moved to another state and contact was lost. Figure 1 shows the relationship of this patient's symptoms of neuritis to the intake of various drugs.

Case 2.—A 50-year-old man entered the VA Hospital, Iowa City, on Aug. 22, 1957, because of numbness in both feet and weakness and pain of his left foot and leg. This patient had been seen on six occasions at this hospital since Oct. 9, 1954, because of chronic, active glomerulonephritis. In 1930 he had an upper respiratory infection followed in one month by the appearance of dark urine and swelling of the hands and face. His blood pressure at that time was said to have been "180" mm. Hg. After this episode he had protein in his urine for one year with intermittent hematuria. He had relatively little difficulty from this, and in 1941 he passed an Army physical examination and was inducted. After one year of service the patient was given a disability discharge because of easy fatigability, bilateral costovertebral angle tenderness, and repeated episodes of proteinuria. He had been seen on a number of occasions at other VA hospitals from 1946 until his admission for the first time here in October, 1954.

On his first admission to this hospital the patient had blood pressure readings up to 230/140 mm. Hg, a few hemorrhages in the ocular fundi, a blood urea nitrogen level of 32 mg.%, and urine containing 2+ protein with 8 to 10 red blood cells per high-power field and a few narrow granular casts. The urinary specific gravity was fixed at 1.008 to 1.010.

During the three years between his first and his most recent admission to this hospital, the patient was treated with the alseroxylon fraction of Rauwolfia serpentina, hydralazine in doses up to 400 mg. a day, pentolinium, and mecamylamine hydrochloride in varying doses. The patient's blood pressure was maintained usually within the levels of 170 to 190 mm. Hg systolic and 90 to 110 mm. Hg diastolic, but he had considerable difficulty with drowsiness and lassitude from the Rauwolfia compound and orthostatic hypotension with the ganglionic blocking agents. Because of these symptoms and the difficulty in controlling his blood pressure within safe ranges, it was decided to treat him with hydralazine alone. On Feb. 1, 1957, hydralazine therapy was begun at 100 mg. four times a day, and this was increased to 125 mg. four times a day on March 7,

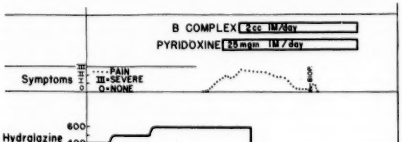

Fig. 2 (case 2).—Relationship between drug administration and pain of polyneuritis as estimated by need of anodynes. Biopsy of left gastrocnemius muscle was done on 54th day of hospitalization. Patient was discharged on 83rd hospital day.

1957, when he was seen as an outpatient (fig. 2). He was seen again as an outpatient on June 6, 1957, and on July 11, 1957, at which time the hydralazine dosage was increased to 150 mg. four times a day. One month later, on Aug. 11, 1957, the patient stated that he noticed a suddenly appearing weakness of his left foot. Three days later he began to notice pain in his left leg and foot, and numbness developed in his right foot at about the same time. The pain was so severe that he was hospitalized in his home town prior to his admission to this hospital. There was no history of trauma to the leg or spine. He had taken only small amounts of aspirin in addition to the hydralazine since Jan. 6, 1957.

Although he had imbibed much alcohol prior to 1955, he had done little drinking since that time. He had lost no weight, and he had had no recent infection. He knew of no exposure to heavy metals, had never had diabetes mellitus or symptoms of that disease, and had had no skin eruptions.

Physical examination on admission revealed a well-developed, slightly obese man who was in acute pain. He was alert and cooperative. The eyes were not remarkable, but the ocular fundi revealed grade 2 arteriolar sclerosis with moderate arteriovenous nicking and generalized attenuation of the arterioles. No exudates or hemorrhages were seen. The skin was normal. The heart was enlarged on the left side, and the second aortic sound was very loud. No murmurs were present. The blood pressure ranged between 240/140 and 210/130 mm. Hg in the arms. There were excellent femoral pulsations. The abdomen had an incisional scar in the right lower quadrant. Neurological examination revealed left peroneal palsy with atrophy and lack of active motion in the left tibialis anterior, extensor digitorum longus and brevis, and the extensor hallucis longus muscles. Bilateral hyperreflexia in the arms and legs and unsustained clonus at the ankle were present and had been present on previous admissions. No abnormal reflexes were noted. There was stocking-type hypesthesia to the junction of the upper and middle third of the legs bilaterally. No abnormal neurological findings were noticed in the upper extremities.

Laboratory studies on admission revealed the white blood cell count to be 10,900 per cubic millimeter with normal distribution of cells. Hemoglobin level was 10.3 Gm.%, as it had been on previous admissions. Urine values were the same as on his first admission. The hematocrit was 41 vol.%, blood urea nitrogen level 40 mg.%, creatinine level 3.7 mg.%, serum sodium level 130 mEq. per liter, potassium level 4.9 mEq. per liter, chlorides level 111 mEq. per liter, and carbon dioxide content 21 mEq. per liter. Serum cholesterol level was 218 mg.%. Several cultures of the urine for bacterial growth were negative, as were three preparations of the peripheral blood for L. E. cells. Blood culture showed no growth. Lumbar puncture showed normal pressures, one cell, and normal sugar, chlorides, and protein levels and gold curve. A test for urinary coproporphyrin was negative. Electrocardiogram showed signs of early left ventricular hypertrophy. The chest film revealed slight rounding of the left ventricular border. Blood sugar level was normal. Biopsy of the left gastrocnemius muscle revealed only atrophy of the muscle fibers. A retrospective diet analysis by the hospital dietician suggested that the patient had had a low-normal intake of B-complex vitamins for six months before admission.

The patient was treated with 25 mg. of pyridoxine given intramuscularly each day from the day of admission, and 12 days after admission daily injections of B-complex vitamins were begun. Hydralazine therapy was continued for 19 days after entry to this hospital. By the 33rd day the patient's pain had decreased considerably in amount, and by 40 days after admission there was active motion in some of the previously paretic muscles. By the 62nd day of hospitalization the patient was no longer taking any anodynes for leg pain and was able to walk with a fairly normal gait. At this time a strength-duration curve of the left tibialis anterior muscle was abnormal, but it became normal by the 75th day of hospitalization (fig. 3). His blood pressure elevations were moderated first with interrupted courses of therapy with chlorothiazide, but when his blood urea nitrogen level rose during this therapy (to 82 mg. per 100 ml.), chlorothiazide was withdrawn. Eventually, he was treated with reserpine alone. His arterial blood pressure values stabilized in the range of 160/105 mm. Hg, and he left the hospital on the 83rd day after admission. When last seen on Jan. 16, 1958, the patient's neuritis was remarkably improved and he had only a minor degree of paresis in his extensor digitorum brevis muscle and some residual numbness of the toes of his right foot.

Comment

Schroeder has discussed recently the metabolism of hydralazine in detail.[2] He states that the drug, besides being a chelating agent, is a carbonyl reagent and forms easily dissociable complexes with sulfhydryl groups on cystine, gluthathione, 2, 3-dimercaptopropanol, and other simple mercaptans. It is an antienzyme for several systems, including known or suspected pyridoxal enzymes, such as DOPA carboxylase and histaminase. Although hydralazine does seem to interfere with conversion of pyridoxal to its metabolite 4-pyridoxic acid, it is not known whether it causes clinical deficiency of vitamin B_6 to develop. Isoniazid, chemically similar to hydralazine, promotes the excretion of a pyridoxal-isoniazid complex in the urine of patients taking the drug. When isoniazid is given in large doses to nonalcoholic tuberculous patients or when it is given in moderate doses to alcoholic patients, peripheral neuritis frequently develops, presumably because of pyridoxine deficiency.[3]

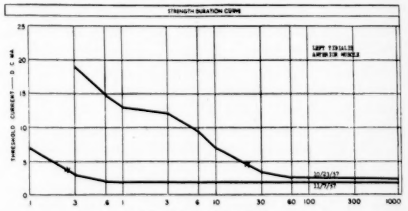

Fig. 3 (case 2).—Strength-duration curve of left tibialis anterior muscle. Curve taken on Oct. 23, 1957, shows (from right to left) an early upward rise and discontinuities. Chronaxy is 20 msec. This is curve of denervation. Curve of Nov. 7, 1957, shows chronaxy of 0.2 msec., and shape of curve is normal.

A cause and effect relationship between hydralazine administration and the development of peripheral neuritis is strongly suggested in these two patients. The first patient was in this hospital for 11 weeks before the neuropathy developed. During this time he was on a diet containing 500 mg. of sodium per day, but with adequate vitamins. The patient did not lose weight. There was no known infection during this time. Tests of the urine on several occasions were negative for bacterial growth. There was no evidence of diabetes mellitus or other metabolic abnormality, and the patient had had no unusual medicament prior to the development of his neuritis. More important in establishing hydralazine as the cause of this patient's difficulty was his gradual response to pyridoxine and his rapid relief of symptoms when hydralazine therapy was stopped.

The clinical course of the second patient's peripheral neuritis also suggests that hydralazine was an etiological factor. This patient had been followed over 46 months by us. Although he had been a moderately heavy drinker of alcohol in the past, he had drunk little alcohol in the 12 months prior to his present admission. His state of nutrition was good. There had been no intercurrent infections. The only drugs taken were those described in his history. Hydralazine had been taken regularly in large daily doses for nine months. This patient, like the first, had no history of metabolic disease, hematoporphyrinuria, collagen disease, or neoplasia. The patient's chronic glomerulonephritis had been slowly progressive over many years, and, except for the significant increase in arterial blood pressure and in frequency of headaches, no other problem had arisen from this disease. Again, the patient's response to withdrawal of hydralazine was dramatic, for pain became much less severe in seven days and had practically disappeared in three weeks after the drug therapy was stopped. Neither patient exhibited cheilosis, glossitis, seborrheic dermatitis, or unusual depression—signs reported to occur during experimentally produced pyridoxine deficiency in man.[5] Anemia, also observed in human pyridoxine deficiency, had been present before hydralazine therapy was started in the second patient and was apparently not aggravated by the drug.

The dietary intake of pyridoxine in both patients was probably at the lower limit of estimated daily requirements,[6] and this factor may have played a role in the development of the neuritis. The first patient was on a diet containing approximately 1 mg. of pyridoxine per day for many weeks. He was not given vitamin supplements until after the neuritis appeared. The second patient had peculiar dietary habits. Although married, he frequently dined away from home on a diet adequate in calories and with approximately 1 mg. of pyridoxine each day, as calculated by the dietician. Even though such a retrospective analysis is fraught with error, particularly when the intake of pyridoxine is estimated, it is probable that this patient did not receive a surplus of vitamin B in his diet. On the other hand, there is no evidence that these patients actually received a diet grossly deficient in vitamin B_6. Their income was at, or above, the average for our patient population, and their general state of nutrition was good.

It is possible that the production of polyneuritis after hydralazine therapy may be dependent on at least two factors: (*a*) long-continued large daily doses of the drug, and (*b*) a relatively low intake of vitamin B_6. However, since these factors are probably interrelated, it may be postulated that the neuritis could be prevented by vitamin B_6 supplementation when large doses of hydralazine are given. The neuritis might appear at times with smaller doses of the drug if dietary vitamin B_6 were in the lower range of normal, as has been suggested with isoniazid.[3]

There is no concrete evidence to support the idea that this drug interferes with any other vitamin B preparation, although to our knowledge this has not been explored. There is no information to support the view that carbohydrate metabolism is disturbed in any way.

These two case reports, added to the literature on the subject, suggest that toxic reactions to hydralazine can be grouped into three general categories: (1) acute or cardiovascular effects, (2) connective tissue, blood, and skin reactions, and (3) polyneuritis syndrome.

Acute Cardiovascular Effects.—Such reactions as tachycardia, nasal stuffiness, occipital headache, dyspnea, malaise, anxiety, nervousness, retrosternal distress, peripheral edema, and, at times, angina pectoris, can be ascribed largely to the effect of the drug on the cardiovascular system. They may be caused by the release of "histamine-like" substances, secondary to inhibition of histaminase by hydralazine[7] or to the central depressor action of the drug.[8] Tingling in the extremities, as noted by Moyer,[9] and the transient paresthesias mentioned by other authors[10] after intensive administration of the drug, likewise, are probably secondary to this cardiovascular effect.

Connective Tissue, Blood, and Skin Reactions.—Minor musculoskeletal symptoms frequently occur with hydralazine therapy without other signs of serious disease.[11] In an occasional patient these symptoms may be severe enough to necessitate stopping the drug therapy, but generally they are mild and tend to disappear as therapy is continued.

A more serious disorder, characterized by arthritis, pancytopenia, fever, various skin lesions, pericardial and pleural effusions, increase in serum globulin level, false-positive serologic tests for syphilis, and positive lupus erythematosus (L. E.) tests on peripheral blood, has been demonstrated to be caused by hydralazine, usually when it is given in large amounts for long periods. Morrow, Schroeder, and Perry[1] did not believe that this hydralazine-produced lupus erythematosus–like reaction was caused by a hypersensitive state. They felt it was better explained by depletion of a trace metal or by an imbalance between essential and abnormal trace metals, in view of hydralazine's known chelating ability. Dustan and co-workers[12] likewise objected to classifying this syndrome as a hypersensitivity state, chiefly because some of their patients were able to resume taking the drug at a lower dose without recurrence of symptoms. They also felt that it was of significance that the syndrome occurred in persons with no allergic history and that it appeared when the doses used were very large and therapy prolonged.

On the other hand, the clinical picture of the disorder, its relation to other rheumatic states (particularly to lupus erythematosus), and the prompt remission of symptoms when the drug is withdrawn have caused much speculation as to whether this complication indeed may represent a hypersensitivity reaction.[12] Reynolds and Caldwell [13] reported a patient who developed tachycardia and blood pressure elevation when first given hydralazine, acute rheumatic symptoms when the drug was given a second time one month later, and the clinical picture of acute rheumatoid arthritis in four days when the drug was given a third time six months after the second course of administration. A positive blood L. E. cell test was not obtained. However, these authors felt that this patient's reaction to the drug was of the lupus erythematosus type. They also considered the small dose and brief period of therapy necessary to reproduce the symptoms as strong evidence against both the toxicity and depletion hypotheses. Slonim [14] also reported a patient who had an exacerbation of symptoms of the hydralazine lupus erythematosus–like disease after a total of only 150 mg. of the drug had been taken in three doses.

If sensitization to hydralazine is responsible for the lupus erythematosus-like syndrome, recorded observations make it appear that the hypersensitivity is of a complex and unusual type. Nevertheless, our experience with this syndrome makes the hypersensitivity explanation a tempting one but does not settle the issue. We have observed six patients develop this syndrome, all after taking relatively large doses of the drug. The lowest dose which caused these symptoms to appear initially was 400 mg. per day continued over two and one-half months. Three of these patients were given this agent a second time, and in each instance a recurrence of symptoms appeared in four days to three weeks. A most dramatic example of this was seen in a 54-year-old woman who was readministered 25 mg. of hydralazine twice a day six months after the acute symptoms of hydralazine lupus erythematosus–like disease had subsided, although L. E. cells were still present in the blood. Two days later, without our knowledge, she began a transcontinental automobile trip. After traveling for one day in the bright sun of the Mojave Desert and having had a total dose of 300 mg. of hydralazine, she developed fever, prostration, and a severe erythematous eruption over the exposed parts of her body. Hydralazine therapy was discontinued, and cortisone was given. The patient recovered gradually in a fortnight.

Blood dyscrasia other than that associated with the hydralazine lupus erythematosus–like syndrome has been reported after hydralazine therapy, [15] but this is rare. Skin rashes of an erythematous nature, not associated with the rheumatic syndromes, have been reported [11]; however, they are seldom a problem in the usual clinical use of hydralazine.

Polyneuritis Syndrome.—Polyneuritis syndrome, as described in this communication, may appear after long therapy at high-dosage levels of hydralazine. It is produced possibly by interference with pyridoxine metabolism; it is readily reversed with withdrawal of the drug, and, perhaps, with pyridoxine dietary supplementation.

In the two patients presented there was no evidence of the hydralazine lupus erythematosus–like disease. L. E. cell preparations in both cases were negative on several occasions, and there was no evidence of hypergammaglobulinemia, positive cephalin flocculation tests, arthritis, fever, skin rash, false-positive serologic tests for syphilis, or involvement of pleural or pericardial linings. Likewise, the blood pressure elevation in both patients failed to show the good response to hydralazine therapy usually seen in association with the lupus erythematosus–like reaction. This evidence, the subsequent course of the patients, and the demonstration of interference with vitamin B_6 metabolism by hydralazine in vivo [2] suggest that polyneuritis may occur as a complication separate from the well-known lupus erythematosus–like syndrome.

Although no instance of the neuritic complication in man has been reported in the English literature, Comens [16] described convulsions and central nervous system symptoms in dogs treated with large doses of hydralazine for long periods. He noticed also that some dogs were unable to stand and ascribed this to weakness. Most of these dogs developed anemia, altered electrophoretic pattern of the serum proteins, leukopenia, hypergammaglobulinemia, hypocholesteremia, and L. E. cells. However, there is no information regarding possible pyridoxine deficiency as a cause of the convulsions or possible polyneuritis to account for the animals' difficulty in standing.

The incidence of polyneuritis after hydralazine therapy must be quite low. In about 700 patients treated with hydralazine in our hospitals during the last five years, most with low-dosage therapy, only the two patients described have been known to develop peripheral neuritis. In this same group, only the six patients mentioned above have been known to develop the lupus erythematosus–like syndrome.

Summary and Conclusions

Two patients developed signs and symptoms of peripheral neuritis while being given large doses of hydralazine. Because hydralazine is known to interfere with pyridoxine metabolism in vivo and has chemical actions similar to isoniazid, it is suggested that the polyneuritis was secondary to the hydralazine ingestion.

Adverse reactions to hydralazine may be classified broadly into three categories: (1) those affecting the cardiovascular system acutely, (2) those producing connective tissue, blood, and skin disorders, and (3) those producing polyneuritis. If peripheral neuritis appears in a patient under treatment with large doses of hydralazine, the drug should be considered as a possible causative or precipitating factor, especially if pyridoxine intake is low. Until more precise information is gained concerning the etiology of polyneuritis occurring under these circumstances, hydralazine therapy should be discontinued and the patient should be given pyridoxine until maximal recovery occurs.

Dr. David M. Paul supplied the strength-duration curves depicted.

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REHABILITATION IN RESPIRATORY INSUFFICIENCY.—Greatly expanded knowledge of the physiology and biochemistry of respiration, together with the technical skills developed in the care and rehabilitation of patients with respiratory paralysis due to poliomyelitis, now make it possible to apply an effective method of total care for the treatment of patients with severe respiratory insufficiency due to a great variety of causes. The fundamental principles are essentially the same in the treatment of all disorders in which there is inadequate pulmonary ventilation associated with respiratory acidosis, disturbed metabolism right-sided heart strain or failure and accompanying psychobiological changes. The first essential is adequate respiratory assistance to relieve the patient of the work of breathing and to correct respiratory acidosis. This may require tracheostomy, artificial respiration for varying periods of time, then gradual reduction in respiratory assistance, a graduated exercise and strengthening program and the whole gamut of services included in the concept of rehabilitation. While this regimen of management does not include any new methods or concepts, it does involve the coordinated application of technics which are usually utilized as separate treatment procedures or as brief supportive measures without adequate understanding of the needs for full restitution of function. When the available technics are applied in a well-coordinated manner, the prognosis for recovery can be very remarkably changed for the better in seemingly hopeless situations.—Leon Lewis, M.D., Application of Rehabilitation Technics in Respiratory Insufficiency, *Archives of Physical Medicine and Rehabilitation*, March, 1958.

STUDY OF 1-PHENYL-2-AMINOPROPANE ALGINATE (LEVONOR), NEW ANORECTIC

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and
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A group of 80 overweight patients who were on a diet designed to reduce weight received, in addition, one 5-mg. tablet of 1-phenyl-2-aminopropane alginate three times a day. This drug was found, in animal experiments, to produce a delay of the feeding reflex without significant stimulation of motor activity. In the human subjects studied, the combined treatment was accompanied by a mean weight loss of 0.9 kg. (2 lb.) per week. The doses used in this experiment did not cause untoward side-effects.

Although a few physicians maintain that the relationship of overweight to serious health impairment is casual, not one denies that the patient who keeps his weight within a normal range will usually experience better health and longer life.[1] Unfortunately, no simple method has yet been found to help the patient regain and maintain an ideal weight through correction of faulty food habits and regulation of food intake. Such factors as heredity, environment, traumatic disturbances, changes in physical activities, and, rarely, endocrine imbalance, are variables that must be taken into consideration in the planning of any weight reduction program.

Every physician recognizes what is necessary to bring about a loss of excess weight: restriction of the diet to bare essentials of proteins, vitamins, and minerals, which causes burning of the stored fat as the chief source of energy. Inevitably, when food intake is restricted sufficiently to induce a negative energy balance, a weight loss ensues, unless, of course, physical activities of the patient are restricted abnormally. Nevertheless, control of appetite is not easy, and "more difficult than the prescription of a diet is keeping the patient on the prescribed program." [2]

Drugs for Suppression of Appetite

Ideal Qualities.—A recent survey [3] reveals that a majority of physicians consider the use of a drug a prerequisite during the initial stage of dieting to help the patient control his intake of calories. By consensus, the ideal drug for treatment of patients who overeat has the following characteristics. 1. It is safe. Its physiological price is low, that is to say, it causes no disturbance of emotional and psychic balance, nor should it require routine use of barbiturates to counteract excessive stimulation. 2. It is effective in appetite suppression. 3. It provides minimal central nervous system stimulation without psychic excitation. 4. It is suitable for use late in the day without interference with normal sleep pattern. 5. It is well tolerated and does not cause constipation. 6. It is economical, with price suitable for immediate and maintenance dosage.

Drawbacks of Drugs Commonly Used.—In an analysis,[3] which included the study of 1,267 overweight patients, 909 were under treatment with both diet and drugs, only 321 by diet alone, and merely 37 by drug alone. Significantly, it was found that although anorexigenic drugs were used extensively most of the physicians interviewed were extremely critical of the difficulties associated with their use, especially in patients who had recently acquired the excess weight. The chief drawbacks were (1) overstimulation followed by weakness, fatigue, depression, and morning anorexia; (2) insomnia, restlessness, and emotional disturbances requiring the use of barbiturates; (3) failure to suppress night-time urges to eat and drink; (4) constipation; (5) expense; and (6) unpredictability of "timed-release" forms of medication in vivo. In brief, the side-effects appear to be the most persistent stumbling block encountered in the use of drugs to curb the appetite.

In recent years [4] various compounds belonging to the sympathomimetic amine group have been used clinically for the suppression of appetite. Strangely, the property commonly shared by these optically active compounds is one of psychic stimulation, while the appetite-suppressing factor is secondary and highly variable. For this reason, the clinician is skeptical as well as friendly toward any new compound that can be demonstrated pharmacologically to exert appetite suppression.

A New Anorectic

Recently, a new agent, 1-phenyl-2-aminopropane alginate (Levonor), has been found to delay the feeding-reflex in animals, with negligible stimula-

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tion on the psychic cerebral centers. It is a well-characterized substance identifiable by its distinctive infrared and x-ray spectrums.[5] Studies were done of its acute toxic effects in the oral form (on mice under controlled environmental conditions of temperature and relative humidity) in order to compare the new substance with several common amphetamine compounds. The results indicate that 1-phenyl-2-aminopropane alginate is one-tenth as toxic as dextro amphetamine sulfate, on the basis of the weight of the respective salts. According to another commonly accepted method of comparison (pressor amine/pressor amine), the 1-phenyl-2-aminopropane alginate was one-fifth as toxic as the dextro amphetamine.

A critical test of the effectiveness of the new drug in suppressing appetite was performed in male monkeys (Macaca rhesus). These animals are normally voracious eaters. After 24 hours of fasting, the monkeys were given 1-phenyl-2-aminopropane alginate orally in doses ranging from 1 to 5 mg. per kilogram of body weight, and the results were pronounced suppression of appetite without overstimulation. No side-reactions, such as hyperactivity, tremors, or jitteriness, were observed.

Determinations of anorectic effect of 1-phenyl-2-aminopropane alginate and four other anorectic drugs were made in dogs.[6] Twenty mongrel dogs, individually caged, were observed while normal feeding habits were stabilized during the four days preceding treatment. During this period each of the animals received 0.6 kg. of food daily, which they consumed five minutes after the food was offered. Water was given as needed. Each drug was administered orally, in capsule form, once daily for three days. Food was offered exactly one hour after each drug was given and an interim of four days allowed between the first and second parts of the cross-over tests, to obviate any effect of the treatment period. The dogs were observed immediately after treatment and watched carefully for six hours after feeding. Again, they were observed for four days after the last treatment in the second part of the trial.

The drugs used in this test, at dose levels of 5 mg. per kilogram, were levo amphetamine sulfate, dextro amphetamine sulfate, phenylpropanolamine, and 1-phenyl-2-aminopropane alginate. These tests clearly demonstrated the superiority of 1-phenyl-2-aminopropane alginate, since it produced pronounced anorexia that persisted for more than three hours. Signs of hyperexcitability, characteristic of patients given the other preparations tested, were notably absent in the subjects given 1-phenyl-2-aminopropane alginate.

In addition to these animal studies, preliminary clinical observations, made on more than 173 patients [6A] over periods of at least 12 weeks, were most promising. Since the side-effects of most anorectics militate against the long-term treatment of the overweight patient, we undertook a clinical study to evaluate the new agent.

Selection of Patients and Procedure

The procedure in the selection and preparation of our patients has been as follows.

First, a thorough physical examination is performed. This prerequisite, given at the start of treatment, helps to convince the patient of the seriousness of the problem and the importance of his keeping on the restricted diet. It also reassures the patient that the physician has not overlooked the possibility of some obscure glandular condition. Further, it helps persuade most patients that they are physically fit to withstand the rigors of dieting and thereby reduces the number of alibis at subsequent visits to excuse the lack of cooperation.

Second, explanation and encouragement are given. The cause-and-effect aspects of overweight are thoroughly discussed and the prescribed diet explained in detail. Success depends to a high degree upon the patient's understanding the principle of the treatment, namely, to provide the necessary food elements yet remove excess fat. Of greater importance, the patient must realize that following the diet does not cause "weakening." Whenever appetite-suppressing drugs are prescribed, the patient should be instructed concerning their mode of action and told what to expect by their use.[7] Since misconceptions concerning diet are so varied that the physician cannot anticipate all, the patients are encouraged to ask questions.

Third, regular check-up visits are required. Most patients are less apt to cheat if they know they must face the doctor's scales at regular intervals. Frequently, these visits have given us an opportunity to give additional education and encouragement as well as to answer any new questions that the patient may have. Many patients benefit greatly by learning about the plateaus of weight loss and are helped immeasurably to achieve self-discipline through these periodic conferences.

Fourth, appetite-suppressing drugs are used. Since the physician is concerned with both the patient's comfort and the success of the regimen, in most instances we have recognized the important role that appetite suppressants can play in helping to reduce caloric intake. By obviating the martyrdom of unsatisfied hunger during the early days of food restriction, the use of appetite suppressants helps to get the patient started on the right path toward recovery without the usual frustration and self-pity that accompany a low-calorie regimen.

Fifth, post-weight-loss procedures are followed. Overweight is a chronic affliction prolonged over a life span and requires close observation similar to

that of diabetes mellitus. Each patient is impressed with this concept. Each is informed that weight loss is only part of the requirement and that maintenance of a desirable weight is even more important."

Weight loss may be reasonably gradual, and once the ideal weight is achieved, frequent observation is necessary to maintain the patient's weight at the desired level. Throughout his lifetime the patient should weigh himself weekly at the same time and under the same conditions. If a gain is seen, the diet must be curtailed immediately and this regimen continued for a few days until the ideal weight range is restored. If weight gain is over 5 lb., the patient is advised to see his physician.

Results

Five-milligram tablets of 1-phenyl-2-aminopropane alginate were given three times a day, one-half hour before meals. Many patients received an added dose at 8 or 9 p. m. to curb the "television" or "bedtime" snacks. There were no signs of restlessness from this late dosage schedule. Many patients had previously been on therapy with amphetamines or amphetamine-like drugs with diet and had little success. Subsequently, these patients were given the new drug with encouraging results, and, in general, they were enthused about the control of appetite and lack of side-effects. In contrast, a small number of patients (approximately 6%), who were accustomed to the "lift" from the amphetamines, either alone or in combination with barbiturates, were difficult to manage with 1-phenyl-2-aminopropane alginate and considered failures.

The patients were seen on an average of every two weeks. Laboratory studies included complete blood cell counts and urine analysis on all patients; a representative number of patients also had basal metabolic rate and glucose tolerance studies. On return visits special attention was given to any changes in weight, heart rate, and blood pressure. The patients were carefully questioned as to the results of the new drug in controlling appetite, its effectiveness as compared with previously used anorectic agents, and the presence of any side-effects.

The average weekly weight loss for patients taking 1-phenyl-2-aminopropane alginate was 2 lb. There were no adverse changes that affected either the blood pressure or the heart rate. On the contrary, many hypertensive patients exhibited a reduction in blood pressures after weight loss. There was a remarkable absence of any side-effects. A single dose that is triple the usual 5-mg. dose causes no significant change in the blood sugar levels (table 1).

Our studies have defined the limitations as well as the indications for the use of the new anorectic. It can be used for a patient who has never taken amphetamines or amphetamine-type drugs (such as phenmetrazine or dextro amphetamine sulfate). It can be used for a patient who responds unfavorably to amphetamine drugs with such symptoms as sleeplessness, nervousness, tension, and a tight feeling in the neck. Since no effects have been observed on blood sugar levels nor on central vasomotor reflexes, the new agent is used in persons with diabetes mellitus and hypertension and in pregnant women.

When amphetamine is contraindicated late in the day, the new anorectic can be used adjunctively, in the evening, without causing insomnia. It also may be given in the evening for appetite control after a morning "timed-release" capsule effect has dissipated. It can be used as an adjunct when the amphetamine dosage cannot be increased due to its side-effects. In such instances, 1-phenyl-2-aminopropane alginate effectively suppresses appetite. Except as adjunctive therapy, the new anorectic is of little value in treating the depressed obese patient and the patient dependent on the analeptic effect of amphetamine for psychic stimulation.

TABLE 1.—*Blood Sugar Changes After Administration of 1-Phenyl-2-Aminopropane Alginate*

Case, No.	Diagnosis	Dose, Mg.	Blood Sugar Level, Mg./100 cc.		
			Fasting	At 1 Hr.	At 2 Hr.
1.....	Normal	15	89	82	86
2.....	Normal	15	112	118	94
3.....	Mild diabetes	15	168	144	148

Glucose tolerance tests, cholesterol and cholesterol ester determinations, and basal metabolic rates showed variable results. In general, these tests gave no indication of therapeutic needs. A few patients were found to have subclinical diabetes mellitus. These patients, like the others, responded to therapy, and their glucose tolerance curves returned to normal in accord with weight reduction. Rarely, a low basal metabolic rate and hypercholesteremia were found, which indicated the need for the addition of thyroid to the regimen.

Three case histories will serve to illustrate how 1-phenyl-2-aminopropane alginate can be used either with a strictly prescribed diet or with simple curtailment of food. A fourth shows a situation in which the new agent was not suitable.

Report of Cases

CASE 1.—A 15-year-old girl had been overweight, weighing 165 lb. (74.8 kg.), since an appendectomy 26 months previously. Since then she had gained 42 lb. (19.1 kg.). She had been overfed during convalescence, and patterns of excess eating and diminished exercise had been well established. Her obesity had forced her into social, athletic, and emotional retirement. Previous efforts at weight reduction had failed because of parental pressure and an inability to tolerate anorexigenic drugs.

A complete reorientation was attempted with both patient and family. Dietary reeducation was undertaken and gentle but firm instructions given. Therapy with 1-phenyl-2-amino-

propane alginate, 5 mg. three times a day before meals, was started. The patient was surprised and pleased to find that her appetite was curtailed without any of the expected side-effects. In 11 weeks this patient lost 24.5 lb. (11.1 kg.). All activities have been resumed, and the outlook for attainment and maintenance of ideal weight appears promising.

CASE 2.—In a 48-year-old male, frequent business lunches and dinners and marked curtailment of physical activities had resulted in a weight gain of 28 lb. (12.7 kg.) during the preceding 12 years. This had been insidious, and the patient always felt that it could easily be reversed. When he found it could not he asked for help, realizing that his indigestion, shortness of breath, and fatigue were directly related to his excess weight. He was very serious in his desire to lose weight but presented the problem of business meals and enforced physical inactivity.

We encouraged the patient to take up golf and to walk as much as possible. After careful study of the patient's eating habits, we suggested that he not mention his diet to colleagues or clients since this encouraged baiting and overeating. We prescribed 1-phenyl-2-aminopropane alginate, 5 mg. three times a day half an hour before each meal, to help him follow his diet. The patient quickly discovered that he could follow his regimen easily without eliciting comment as long as he made no mention of it. He experienced no side-effects. In 10 weeks, the patient lost 24 lb. (10.9 kg.), and during the five weeks preceding this report he has maintained the loss without difficulty. This case exemplifies the value of careful explanation of the means of overcoming eating problems as well as the usefulness of a suitable anorectic that reduces the appetite without any other effect.

TABLE 2.—*Average Weight Loss of Eighty Patients Taking 1-Phenyl-2-Aminopropane Alginate*

Av. Weight Loss/Wk., Lb.	Patients	
	No.	Total
0.1-1.0	23	28.8
1.1-2.0	27	33.8
2.1-3.0	15	18.7
3.1-4.0	8	10.0
4.1-5.0	4	5.0
5.1-6.0	3	3.7
	80	100.0

CASE 3.—A 44-year-old male had received a "timed-release" type of medication in the morning for control of appetite during the day, but he could not take the drug in the evening for control of night-time craving. We prescribed one tablet daily at 7 p. m. of 1-phenyl-2-aminopropane alginate. This allayed the evening hunger and permitted the patient to restrict his caloric intake remarkably well without emotional disturbance or sleeplessness. The results were excellent.

CASE 4.—A 41-year-old female during the past eight years had received frequent intermittent treatments for recurrent obesity. During the past four years, she had taken fairly regularly 40 mg. of dextro amphetamine sulfate and 60 mg. of phenobarbital each day. She liked the "lift" these drugs gave her and complained when they were withheld. A diet was prescribed for her, and she was given 1-phenyl-2-aminopropane alginate, 5 mg. three times a day. She lost 7 lb. (3.2 kg.) during the next eight weeks, a better result than she had experienced in the past, but she complained so much about the lack of stimulation that subsequently therapy with 1-phenyl-2-aminopropane alginate was stopped, and she returned to the old regimen. The patient was not suitable for therapy with the new anorectic.

Comment

A group of 80 overweight patients, ranging in age from 15 to 69 years, have been treated with 1-phenyl-2-aminopropane alginate and a properly maintained diet to determine the effectiveness of the drug in controlling appetite. Of the group studied, 70% were females and 30% males. The duration of therapy ranged from 1 to 38 weeks. The average weight loss for the group was 2 lb. (0.9 kg.) per week. A more detailed classification of average weight loss appears in table 2.

Our experience with 1-phenyl-2-aminopropane alginate was highly satisfactory. The incidence of disappointments experienced with anorectics in the past, principally those due to the adverse side-effects of amphetamines, was lessened markedly.

We have been using the amphetamine drugs for appetite control since their introduction more than a score of years ago and recognize that many factors are determinants of their successful use. Both reactions and gradual lessening of effectiveness are limiting factors to be considered in therapy with this group of compounds. We have tried nearly all new appetite suppressants as they have become available because we recognize their potential usefulness, in spite of the limitations that stem from the side-effects. These limitations impose precautions, which include (1) careful selection of patients; (2) explanation and forewarning of possible side-effects; (3) close supervision of each patient; and (4) frequent and gradual adjustment of dosage.

The most common cause of patient complaint is well known by such terms as jitters, nerves, irritability, overstimulation, or nervous tension, according to the vocabulary of the patient. Insomnia is next in the order of discomforts. Other complaints somewhat less common are of constipation, headache, apprehension, exhilaration, palpitation, weakness, fatigue, and, occasionally, nausea and vomiting. Many patients state that since they cannot take the usual appetite suppressants late in the day, they frequently yield to the temptation of evening snacks and night ice box raids, and thus their "cheating on eating" begins.

Since compiling the data for this paper we have had an opportunity to study the findings of another group of investigators in 1,395 cases [3] where 1-phenyl-2-aminopropane alginate was used in conjunction with diet, and the results are in general agreement with our own.

Preliminary studies to be published by us at a later date, in which placebos were compared with 1-phenyl-2-aminopropane alginate, with the use of the double-blind technique, indicate that the patients who were on a diet plus therapy with the new drug lost approximately 1.8 times the weight per week of another group of patients who were also on a regimen of lowered caloric intake but receiving placebos.

Summary

A new drug, 1-phenyl-2-aminopropane alginate (Levonor), was administered, in conjunction with diet, to 80 overweight patients. The average weight loss was 2 lb. (0.9 kg.) per week. We were particularly impressed with the marked reduction in side-effects with the new drug, as compared with our previous experience with other appetite suppressants. The fact that 1-phenyl-2-aminopropane alginate can be administered in the early evening without complaints of interference with sleep is an advantage to both physician and patient, since night-time eating is perhaps the most common cause of "diet cheating."

While 1-phenyl-2-aminopropane alginate appears at least as effective as other appetite suppressants, it seems to be better tolerated and allows for more freedom in adjusting dosage to meet individual patient requirements. We believe, therefore, that this new drug is a valuable and needed tool in helping overweight patients to reduce their caloric intake. On the other hand, the drug is of no value for the depressed obese patient or in cases where psychic stimulation is indicated. Our over-all impression is that weight reduction is better maintained when the loss is achieved at a physiologic and moderate rate.

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The 1-phenyl-2-aminopropane alginate used in this study was supplied as Levonor by Nordmark Pharmaceutical Laboratories, Irvington, N. J.

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PLEUROESOPHAGEAL LINE IN NORMAL CHEST ROENTGENOGRAMS

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The pleuroesophageal line, formerly called the esophageal-pleural stripe, can be seen in about one-fourth of all routine roentgenograms of the adult chest. It is usually 3-5 mm. wide, curving downward and to the left from the apex of the right lung toward the arch of the aorta, but it exhibits many variations. Evidence here presented shows that it is the shadow of a soft tissue plane that separates the right lung from certain other air-filled structures in the mediastinum. It has no pathological or prognostic significance, but its normal variations should be studied and appreciated if false associations of the pleuroesophageal line with symptoms or suspected disease processes are to be avoided.

For several years referring physicians have expressed skeptical curiosity regarding the nature and significance of the narrow oblique line of soft tissue density often seen across the upper mediastinum in the posteroanterior projection roentgenograms of normal chests. This line is usually 3-5 mm. wide and characteristically curves downward and to the left from the right apex toward the aorta. It is the shadow of a soft tissue plane outlined on both sides by air density, and it is projected through the air-filled trachea superimposed on the complex image of the upper portion of the thoracic spine and the manubrium, as illustrated in fig. 1A. There are many variations of contour. Some of the configurations produced by a large air bolus in the esophagus may be quite striking.

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Method

With good roentgenographic technique, with 90 to 120 kvp utilized, this line can be identified easily in approximately 25% of the routine chest films of the adult population. At lower voltages, this image will not be on the film unless the lung fields are overexposed. I have been using high kvp technique for chest roentgenography since 1951, and this technique was made routine practice at this hospital in 1954. All chest films are made at 72 in. distance, 110 kvp with 2 mm. Al filtration, Potter-Bucky grid, and exposure duration of 1/60 to 1/20 second. Only the duration of exposure and milliamperes are changed to compensate for variations of chest thickness. This technique provides three real advantages: 1. It reduces the radiation absorbed by the patient to the minimum, delivering a skin dose of about 20 mr (with scatter) to the thorax of an adult male. 2. It provides penetration of all parts of the thorax and upper abdomen, permitting clear visualization of soft tissue structures of the mediastinum that otherwise would be lost in the opacity of these heavy parts or obscured by the bone structures of the thorax. 3. It permits exposures of relatively short duration, minimizing the blurring of cardiovascular and pulmonary structures which are in rapid pulsation. The pleuroesophageal line is clearly visible only on chest roentgenograms exhibiting good penetration and sharp definition of the upper mediastinal structures. There seems to be a definite trend toward more common use of higher voltages in chest roentgenography, even among nonradiologists. This trend is being accelerated by the efforts being made to reduce radiation exposures in diagnostic radiography. Since more and more physicians are be-

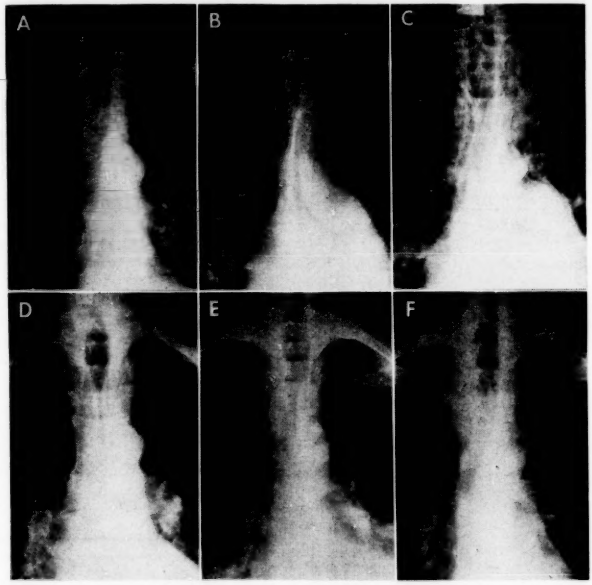

Fig. 1.—*A*, common configuration of pleuroesophageal line forming an arc from right apex toward aorta. *B*, Anteroposterior projection with patient in supine position. Left side of line is accentuated by ink marks; esophageal side is shown in contrast with air and barium. *C* (same patient with pneumomediastinum after an accident), funnel-shaped air column within esophagus is seen through air-filled trachea. Pleuroesophageal line may be identified, and careful inspection of line reveals air between esophageal wall and parietal pleura continuous with tissue planes of neck. *D*, *E*, *F*, effects of large air bolus in the esophagus demonstrated in three different individuals. Pleuroesophageal line is almost vertical, and air column can be followed into lower esophagus through heart shadow. Large air bolus outlines similar septum in left mediastinum and might be called a left pleuroesophageal line.

ginning to notice the pleuroesophageal line and since radiologists in the United States see only a portion of the chest roentgenograms, it is important to disseminate the information concerning this anatomic landmark to all physicians rather than to the specializing group exclusively.

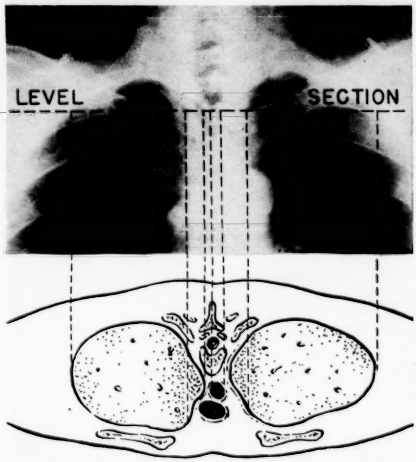

Fig. 2.—Oblique pleuroesophageal line shown in arc from right second rib to aortic arch. Structures of upper thorax are diagrammed in schematic projection of cross-section to illustrate manner in which funnel-shaped air column in esophagus projects through trachea at this level, giving air contrast to esophageal margin of the pleuroesophageal line.

Cause of Pleuroesophageal Line

Most persons retain a small volume of air in the upper thoracic esophagus when they are standing or sitting erect. In this position the heart and the other heavy mediastinal structures are drawn downward so as to produce thinning of the upper mediastinum in its transverse diameter. This traction also produces a slight negative pressure in the upper esophagus that is usually neutralized by entry of a small amount of air. One will then observe in the posteroanterior (or anteroposterior) projection a continuous curved linear shadow of soft tissue density extending from the right apex downward across the second or third thoracic vertebra toward the aorta. Air contrast is present on both sides of the line, which varies from 3 mm. to 8 mm. in width. If air is not present in the esophagus, only the margin of air-filled right lung against the mediastinum can be seen.

Demonstration of Pleuroesophageal Line

In the upright position, the right margin of the adult esophagus lies in direct contact with the upper mediastinal pleura from the thoracic inlet to the azygos vein with only a small amount of muscle and loose connective tissue separating esophageal mucosa from the pleura. Figure 2 presents a diagrammatic cross-section of the upper mediastinum at the level of the pleuroesophageal line, indicating the projection of the two air-contrast margins that form the line when the esophagus contains air. In figure 3, spot films of the esophagus with use of air bolus and barium swallows demonstrate how the retained air, swallowed air, or barium suspension may outline the esophageal margin of the pleuroesophageal line. The air-filled lung provides air contrast against the pleura to form the other margin. This is confirmed in figure 4, which presents an oblique view of the upper esophagus and body section roentgenograms of the upper esophagus, illustrating how the right lung bulges

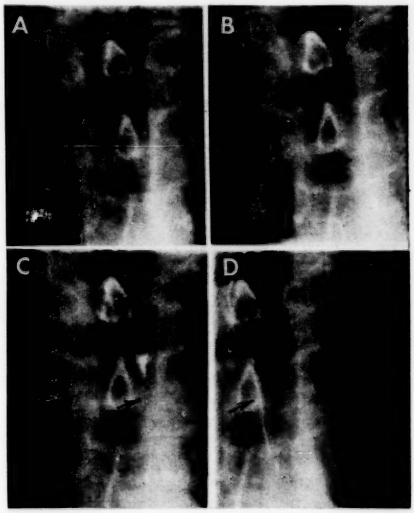

Fig. 3.—During fluoroscopy in upright position, particularly with an image amplifier, pleuroesophageal line may be recognized as elastic septum that responds to dynamics of intrathoracic and intraesophageal pressure changes. *A*, inspiration causes line to move downward toward right hilum. *B*, expiration moves it upward, "squeezing" air column in esophagus. *C*, normal swallow with air and barium mixed shows amount of air usually retained after barium bolus has passed. *D*, air bolus distends esophagus momentarily and lower part of pleuroesophageal line is displaced several millimeters to patient's right.

behind the trachea against the thin septum composed of the esophageal wall, the visceral and parietal pleura, and the connective tissue between.

Cimmino, in 1956, presented 5 illustrations and a brief discussion of the "esophageal-pleural stripe."[1] This term seems unnecessarily compli-

cated. Only two previous publications [2] have attempted to analyze the roentgenographic peculiarities of the upper mediastinum associated with linear markings and projected septums. None of these authors described the variations of the pleuroesophageal line as related to erect position, residual air bolus, swallowing, or respiratory dynamics.

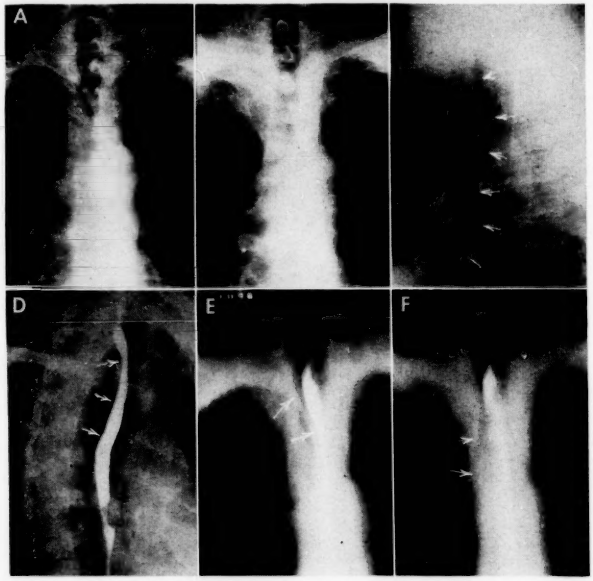

Fig. 4.—*A*, common configuration of pleuroesophageal line, representing septum of soft tissue sandwiched between two air-containing structures: right lung and upper esophagus. *B*, roentgenogram of same patient in supine position. Air in upper esophagus has been swallowed and now only margin or profile of right lung against upper mediastinum is visible through air-filled trachea. *C*, in lateral projection of chest, air may be seen in entire esophagus between spine and trachea if roentgenographic exposure is made while patient swallows or belches large air bolus. *D*, oblique projection of barium-filled esophagus demonstrates barium-contrasted pleuroesophageal line from apex of right lung to crossing of azygos vein. Line is more difficult to identify with air in esophagus. *E*, body section roentgenogram through level of upper esophagus shows apical segment of right upper lobe bulging behind trachea to form air contrast against posterior upper mediastinum. Visceral and parietal pleura, some connective tissue, and wall of esophagus separate air-filled lung from barium to form pleuroesophageal line. *F*, roentgenographic section 3 cm. anterior to esophagus shows pleurotracheal line, plane of tissues comprising tracheal wall, connective tissues, and layers of pleura.

The significance of the air normally retained in the esophagus has not been appreciated. The Drs. Felson [3] illustrated and discussed the mechanism of air-tissue contrast in the projection of roentgenographic images of the mediastinal silhouette. This same mechanism determines whether there will be an image of the esophageal silhouette. The esophageal margins form no image unless the esophagus contains material more opaque or more radiolucent than the soft tissues of the upper mediastinum.

Figure 4*A* demonstrates a typical pleuroesophageal line with the esophageal margin formed by contrast of the residual air bolus in the upright esophagus. As the same patient moves into supine position, he becomes aware of the air and may belch or swallow. Several seconds later when the anteroposterior film of the upper mediastinum (fig. 4*B*) is exposed, there is no air to form an air contrast of the esophageal line. There is no line; only the pleuromediastinal margin from the

thoracic inlet to the azygos vein is seen now. It would not be unreasonable to refer to this as the pleuroesophageal margin under these circumstances, although the esophagus actually takes no part in the formation of the image. When the patient is able to swallow air or belch during the exposure, some form of pleuroesophageal line can be identified in almost every adult and in most children. Many individuals will present bizarre configurations with large air bolus (fig. 1*D*, *E*, *F*). Air may be seen in the esophagus on lateral projection roentgenograms of the thorax if exposure is made during efforts to produce an intentional air bolus (fig. 4*C*).

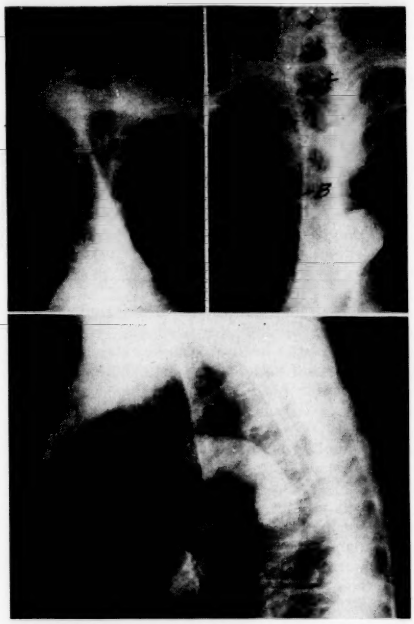

Fig. 5.—Emphysematous lungs producing bizarre septums and marginal contrasts in mediastinum. At point *B* in lordotic and posteroanterior projections is seen thin septum formed by approximated visceral and parietal pleura of right and left lungs. Almost all connective tissue has been displaced from anterior mediastinal space. At point *A* in posteroanterior film, pleuroesophageal margin can be identified, but absence of air in esophagus prevents projection of line. Difference between septate mediastinum and pleuroesophageal line is obvious. Point *C* in lateral projection represents sharp pleuroarterial margin where air-filled lung lies against innominate artery (if gas or opaque material filled artery pleuroarterial line would be seen).

Pathology and Normality

Persons with pulmonary emphysema often have strange linear patterns superimposed on the recognized structures of the mediastinum. The left lung and the right lung often become approximated anterior to the aorta and the innominate artery, displacing the soft connective tissues of the mediastinum until nothing remains in the anterior mediastinal space but a thin sagittal septum formed by the sandwich of pleura between the two lungs. The lungs also may become approximated behind the pulmonary artery. A pleuroesophageal margin is almost always seen, but air is usually absent from the upper thoracic esophagus because of the elevated intrathoracic pressure. The illustrations of figure 5 identify the anterior mediastinal septum formed by approximated emphysematous lungs at B. This eccentric curved line is easily located in both the lordotic and the posteroanterior projections. It is in no way related to the pleuroesophageal margin at point A. The lateral projection illustrated the projection of a sharp air-contrast margin of the anterior profile of the innominate artery because the lungs have replaced the areolar connective tissue that usually fills the anterior mediastinal space. It should be noted that this is considerably below the level at which the pleuroesophageal line is seen in the posteroanterior projection, and there is no reason to confuse the two. The pleuroesophageal line (or margin) carries no diagnostic implication of emphysema.

Conclusions

Although the pleuroesophageal line has no pathological or prognostic significance, it is obvious that the feature and the mechanism of its projection on the normal chest roentgenogram must become familiar to all who are responsible for interpretation of x-ray films. False association of the pleuroesophageal line with symptoms or suspected disease processes must be avoided. When its physiological significance is appreciated and one has became familiar with the normal variations, it is possible to use this landmark in the thorax for the study of real abnormalities of the thoracic inlet and the upper mediastinum.

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SKELETAL HEAD FRAME

A PRELIMINARY REPORT

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In the management of maxillofacial fractures, a skeletal head frame has been devised in an attempt to overcome usual immobilization disadvantages and to provide the necessary extraoral point of fixation frequently required. Placing the head frame takes about 15 minutes. All types of craniomaxillary injuries are amenable to treatment with this skeletal head frame.

Surgeons familiar with the treatment of maxillofacial fractures are aware of the inadequacy of the present method of plaster head caps in obtaining an extraoral point of fixation for reducing and immobilizing fractured bones.

Plaster Head Cap

Numerous appliances have been tried and all were found lacking in one or more ways. The plaster head cap (fig. 1) has been commonly used to provide an extraoral point of fixation. The discomforts of the patient and the complications that often arise from the use of plaster head caps have been detailed by Archer.[1] The following shortcomings are included: 1. It can never be rigidly stable, and it moves in direct proportion with the movement of the scalp. 2. When felt pads or sponge rubber are used over prominent bony areas of the skull, it is common for pressure necrosis in one or more areas to result under the plaster head cap. The more felt or rubber used in relief areas over bony prominences, the less stable is the plaster head cap. 3. Female patients are reluctant to have their hair cut off in preparation for the installation of a plaster head cap. 4. In hot weather, the plaster head cap can be extremely uncomfortable. Oral surgeons and patients frequently find the plaster head cap intolerable. Constant perspiration and unbearable itch precede fungus or secondary infection due to scratching. 5. The routinely applied plaster head cap, extending under the mastoids to take advantage of the undercuts, is bulky, and the patient invariably complains of its weight. 6. A plaster head cap cannot be used on patients with lacerations of the scalp or skull damage and brain injuries associated with fractures of the face. 7. Many patients with facial injuries also have fractured legs or abdominal injuries which make them bedfast. Plaster head caps are contraindicated in these cases because the patient moves his head and greater irritation to the scalp occurs. 8. Osteomyelitis of the skull has been reported after the use of the plaster head cap. Deepithelialized areas can and do result.

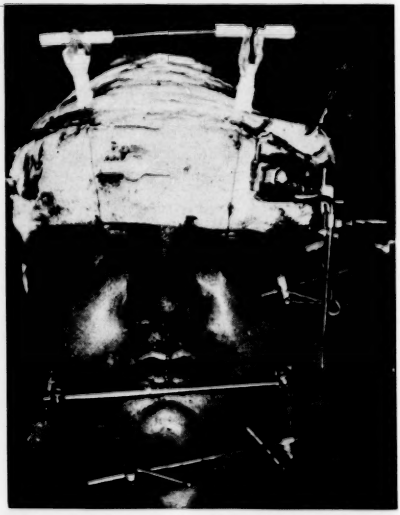

Fig. 1.—Front view of commonly used plaster head cap.

Skeletal Head Frame

In an attempt to overcome these disadvantages and to provide the necessary extraoral point of fixation frequently required in the management of maxillofacial fractures, the authors (an oral surgeon, a neurosurgeon, and a developmental engineer) designed a skeletal head frame which consists of an aluminum frame comprising three curved channel bars and finely turned, adjustable, stainless steel spade drills (fig. 2).

The appliance is held by a burrowing into the cortical bone, lamina externa, in the manner of Crutchfield tongs. Since the finely turned spade drill points readily pierce the scalp with gentle pressure, incisions are unnecessary. Two spade drills are driven into the temporal region on each

side, and a pointed stabilizer, resting against the bone at the top center of the head, provides complete rigid stability. After the frame is placed, which takes less than 15 minutes, the patient is further prepared and draped routinely for the maxillofacial reduction. Roger Anderson pins are placed, and connecting bars are attached to the Roger Anderson appliance. Any other orthopedic, maxillofacial, wire, or neurosurgical device is similarly attached.

In a series of 15 cases the following advantages have been noted: 1. The spade drill points produce no abnormal roentgenographic changes. 2. The inherent tension of the frame prevents the spade drills from becoming loose. 3. The frame may be applied with general or local anesthesia over shampooed, short-clipped hair. 4. All patients were entirely free from pain and unpleasant sensations, because the periosteum was pierced when access to the cortical table was made. 5. The frame weighs 6 oz., but, because of elimination of periosteal sensation, the patient is unaware of its weight. 6. None of the patients developed osteomyelitis. 7. The frame can be used additionally for traction in cervical spine fractures. 8. It can be used for measuring the parameters in stereotaxic neurosurgical procedures, such as chemopallidectomy. 9. The apparatus would appear to be ideal for mass casualty injuries in which the same individual sustains multiple maxillofacial and other fractures and cervical spine dislocation. 10. Even with skull fractures present, shifting the spade drill points to more rigid locations of the calvaria, and the frame is readily adaptable by virtue of the channel bar. 11. Débrided and sutured scalp lacerations do not complicate the use of the frame. 12. This appliance can be used for intranasal and extranasal splinting of fractures. 13. Bars attached to the frame may be used to retain compression dressings and ocular prosthesis.

The pins are stainless, shaped in the typical "spade drill" form, and have a shoulder about ⅛ in. from the point of the pin. Above the shoulder the pin has ringed grooves ⅛ in. apart, similar to Roger Anderson pins, to help gauge the penetration. When the shoulder of the drill point rests against the lamina externa of the skull, no further entry is permitted. The connecting bars running from the head frame to the fracture sites are of the same circumference as the Roger Anderson bars, so that the single wrench fits all of the nuts, increasing the versatility of the appliance.

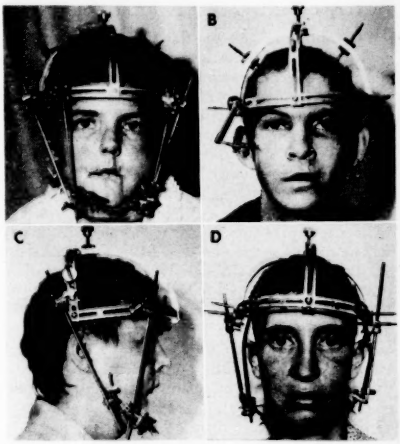

Fig. 2.—Skeletal head frame used in the following cases: *A*, maxillary and mandibular fractures; *B*, depressed zygoma, orbital floor fracture, infraorbital ridge fracture, and fracture of zygomatic arch; *C*, bone graft of bilateral, untreated mandibular fracture in edentulous patient; *D*, facial fractures with skull fracture.

We feel that a spectacular advance in extraoral fixation has been achieved in this device and that it represents a real milestone in the ever-advancing search for improved orthopedic maxillofacial and neurosurgical appliances.

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A MASS SOCIETY.—Today's society is seemingly dominated by what Riesman calls the "other-directed" man, who finds the motivations of his conduct and the end he pursues not in himself, but in the dictation of the group. An age of mass production and mass communication gives birth to a mass society, where the individual is as much standardized as are syndicated columns, TV shows and the products of industry. Few dare to be different, and for good reason—for to be different brings them under the condemnation of the group on whose opinion they form their own opinion of themselves. The idolatry of conformity, of being like everyone else in a group which tolerates only "marginal diversity"; the frenzy with which so many people addict themselves to all sorts of superficial activities or passivities—these and other enslavements of contemporary life originate, at least to some extent, from the need to replace beliefs and values and faith in which man once found security.— F. J. Braceland, M.D., Psychiatry and the Science of Man, Presidential Address, *The American Journal of Psychiatry*, July, 1957.

OPTIMUM AGE FOR SURGICAL CLOSURE OF PATENT DUCTUS ARTERIOSUS

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In order to determine the most favorable time for surgical closure of patent ductus arteriosus, the histories of 66 patients were reviewed. These patients had all been proved by cardiac catheterization, operation, or autopsy to have this condition as the sole cardiovascular anomaly. Three were not operated on. The other 63 were operated on without a death or any serious postoperative complications. Nearly half of the operations were done on patients under the age of 5 years. The data showed that postponing the operation beyond that age implied years of living with a severe handicap and with the danger of life-threatening complications such as heart failure, pulmonary hypertension, endarteritis, and degenerative vascular changes. After the age of 5 years the incidence of these complications increased sharply. Surgical division of the patent ductus provided a permanent cure. The authors recommend that in children under the age of 5 with symptoms of patent ductus arteriosus the closure be done as soon as the diagnosis is established, and that in children who are asymptomatic but known to have the condition the operation be done before the age of 5.

The optimum age for the surgical closure of a patent ductus arteriosus has not yet been clearly defined. A recent review of the combined experience of 49 surgeons with 3,896 patients who were operated on for this lesion suggests that the ideal time to recommend surgical intervention is when the patient is between 6 and 12 years of age unless signs of failure appear.[1] The fact that this policy may not serve the best interests of every patient is suggested by a recent evaluation of our experience with a group of infants and children with proved patent ductus arteriosus who have been cared for at the Columbus Children's Hospital during the past seven years. This analysis of our patients clearly shows that better management could have been afforded these patients by earlier correction of this common cardiovascular anomaly. As has been emphasized previously, deferment of surgical therapy may result in death for an infant whose condition is deteriorating solely from the effects of a patent ductus arteriosus. More often, however, such a delay leads to a continual pattern of growth failure and to recurrent refractory cardiopulmonary symptoms in younger children. Further procrastination exposes the older child to the risk of such serious complications as bacterial endarteritis, irreversible pulmonary hypertension, compromised myocardial reserve, and advanced pulmonary vascular degenerative changes. Familiarity with these facts has stimulated us to reexamine the objectives of the surgical management of this congenital defect and to attempt to define more lucidly the age range during which operation can be performed with maximum effectiveness.

Review of Patients

All patients who were admitted to the Columbus Children's Hospital during the period July, 1950, to June, 1957, who were proved by cardiac catheterization, operation, or autopsy to have a patent ductus arteriosus as the sole cardiovascular anomaly are included in this study. In all there were 66 patients meeting these criteria. Sixty-three of these children were operated on without a death or any serious postoperative complications. Nearly 50% were operated on before the age of 5 years. Eleven were operated on in the first 2 years of life, 19 between the ages of 2 and 5 years, and 33 between the ages of 5 and 16 years. In general the postoperative course was smoother in the younger patients, even though the majority of the infants showed serious symptoms, were grossly underweight, and often suffered from myocardial decompensation. The three patients on whom no operation was done must be considered therapeutic failures since two, although living (10 and 12 years of age), are considered inoperable because of reversal of their ductal shunts, while the third, an infant, died with his condition undiagnosed. These failures should be avoidable today, provided physicians are more cognizant of the manifestations of this disease in early life, make full use of the available diagnostic procedures, and recommend earlier surgical intervention.

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Manifestations of Patent Ductus Arteriosus

Cardiopulmonary symptoms were the commonest abnormalities observed and were present in 49 of the 66 infants and children included in this series. All of the infants were seriously ill at the time when they were admitted to this hospital. Each suffered from one or more of such symptoms as recurrent respiratory infection, inability to feed properly, and excessive irritability and fretfulness; each frequently was noted by his parents to have shortness of breath, tachypnea, and a rapid, forceful heartbeat. Thirty-seven of the 54 children who were over 2 years of age were observed to have exertional dyspnea, easy fatigability, or recurring respiratory infections which required frequent medical attention. Individually and collectively these patients presented a total morbidity, due to their altered cardiorespiratory physiology, that is certainly not inconsequential (fig. 1).

Growth and Development

Thirty-four of the 66 patients, including all 12 of the infants, fell below the 10th percentile curve on a Boston Children's Medical Center anthropometric chart for weight. One infant 2 months of age weighed less than his birth weight at the time of operation. Failure to gain normally was less frequently observed in the older children, although 22 of the 54 patients who were more than 2 and less than 16 years of age also fell below the 10th percentile. The significance of the preoperative evaluation of the weight was enhanced by the postoperative increase in percentile for weight shown by 20 children whose weight was followed from one to

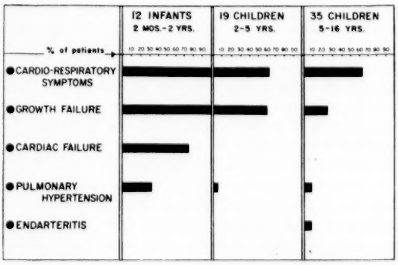

Fig. 1.—Manifestations of patent ductus arteriosus.

five years after operation. In these 20 for whom follow-up information was available, the median percentile for weight was 10 preoperatively and 65 postoperatively. Ten of the 11 patients who fell on or below the 10th percentile curve preoperatively rose above the 30th percentile postoperatively (fig. 2).

Complications Which Threaten Life

The serious complications of a patent ductus arteriosus are by no means limited to the patients in the older age group. Heart failure, pulmonary hypertension, acute and subacute endarteritis, and pulmonary vascular degenerative disease can and do occur in children.

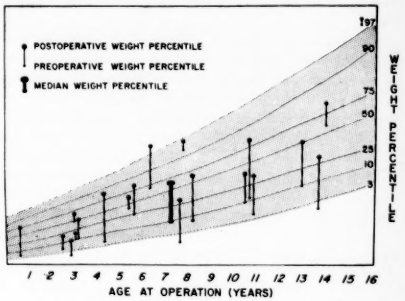

Fig. 2.—Weight change observed in 20 children after division of patent ductus arteriosus (adapted from Boston Children's Hospital anthropometric chart for weight).

Heart Failure.—Nine of the 12 infants in this series showed definite evidence of cardiac decompensation at the time they were admitted to the hospital for diagnosis and treatment. After a brief period of medical management eight of these infants were successfully operated on, while the remaining infant died with no diagnosis given. None of the older children in this series were in heart failure.

Pulmonary Hypertension.—Pulmonary arterial hypertension, with blood pressure ranging from 40/25 to 140/80 mm. Hg, was present in 8 of 10 patients who underwent cardiac catheterization. Four of these patients were less than 2 years of age, and three patients with pulmonary artery pressures equal to or greater than systemic arterial pressures were 10, 12, and 14 years of age. All four of the infants with pulmonary hypertension were in cardiac failure. Only one of the three older children, a 14-year-old boy who had a balanced flow through his ductus, was deemed amenable to surgical treatment. The two remaining older children, aged 10 and 12, already had evidence of reversed flow through the ductus during the cardiac cycle and were deemed to be inoperable. The ductus was divided without incident in all other patients with pulmonary hypertension.

Endarteritis.—Three children, all of whom were over 5 years of age, developed bacterial endarteritis, which was confirmed by blood culture studies in each instance. Diplococcus pneumoniae, Streptococcus viridans, and Stapyhlococcus pyogenes

var. aureus were the causative organisms in the respective patients. Each child was critically ill and one developed multiple septic pulmonary emboli during the course of this illness. All three patients responded satisfactorily to treatment with large doses of penicillin given intravenously, and the ductus was successfully divided four to six weeks after the blood culture tests had reverted to negative.

Degenerative Vascular Changes.—There were no cases of such gross degenerative vascular changes as pulmonary or ductal aneurysm, and the peripheral lung biopsies, which were obtained in several instances, showed no histological abnormalities.

Comment

Physicians agree that when a persistently patent ductus arteriosus exists as an isolated congenital cardiovascular defect it should be surgically closed sometime during childhood. The operation is safe and, when the ductus is divided, provides a permanent cure. The mortality rate which attends this procedure is as low in infants as in children. Analysis of those reports in the literature where the result by age is clearly stated shows that the mortality was 1.1% in 91 infants less than 2 years of age and 1.3% in 378 young children less than 5 years of age, as compared with a mortality of 1.5% in 480 children 5 to 16 years of age (table 1). Although the differences are not statistically significant, these results are particularly impressive when one considers that most of the infants were seriously ill, often with cardiac decompensation, when the operation was performed, whereas the majority of the older patients were relatively asymptomatic. There is little question, therefore, that the obliteration of a patent ductus can be safely carried out in any age group. The determining factor in choosing the optimum time for surgical intervention need not be dictated by the operative mortality but rather by the expected morbidity and mortality that attends the disease itself.

TABLE 1.—*Summary of 949 Cases Where Results by Age After Operation for Patent Ductus Arteriosus Are Clearly Stated*

References	Age, Yr.* <2 Cases, No.	<2 Deaths, No.	<5 Cases, No.	<5 Deaths, No.	5-16 Cases, No.	5-16 Deaths, No.
Jones, J. C.: J. Thoracic Surg. **16**:395, 1947	...	...	17	0	28	2
Gross and Longino[7]	...	...	101	4	213	**3**
Ziegler[2]	8	1	19	1	...	...
Adams and others[3]	15	0	15	0	...	...
Holman and others[6]	5	0	30	0	**33**	**1**
Lyon and Kaplan [13] Ash, R., and Fischer, D.: Pediatrics **16**:686, 1955	4	0	4	0	...	...
	21	0	93	**0**	39	**0**
Hay J. D., and Ward, O.C.: Arch. Dis. Childhood **31**:279, 1956	3	0	32	0	74	1
Glenn, W. W. L., and others: Ann. Surg. **143**:471, 1956	6	0	37	0	60	0
Bauersfeld, S. R., and others: J. Thoracic Surg. **33**:123, 1957	18	0	...	...	...	...
Clatworthy and McDonald, 1957	11	0	30	0	33	0
Totals	91	1	378	5	480	7

* At 2 years the mortality was 1.1, at 5 1.3, and at 5 to 16 years 1.5%. The overall mortality of the 949 patients, under 16 years of age, was 1.4%

A large, functionally patent ductus arteriosus may destroy the very young. Ziegler [2] and Adams and associates [3] have stressed the clinical features of this lesion as it is seen in infants and have emphasized the importance of establishing the diagnosis and proceeding with the closure of the ductus without delay in any infant who shows symptoms. Fortunately the majority of patients do not get into serious difficulty during infancy, but they do experience a considerable morbidity from cardiopulmonary manifestations and physical retardation during childhood. There is little justification for permitting even these minor abnormalities to persist, since they nearly always disappear after closure of the ductus. Adams and Forsyth [4] followed the weights of patients after repair of the ductus and concluded that the rate of growth and the attainment of physical potential were diminished when surgery was performed on patients in late childhood.

With rare exception, all patients with this anomaly who survive infancy and early childhood are exposed to the risk of such complications as superimposed infection, irreversible pulmonary hypertension, and vascular degenerative changes, and after the patient reaches the age of 5 years the incidence of these complications increases sharply.

Although bacterial endarteritis is a particularly feared complication in adults, there has been little written about its occurrence in children. Hubbard and associates [5] in a collected review of 39 cases have found eight instances of endarteritis that occurred in children all of whom were over 6 years of age. Holman and associates [6] reported four cases which occurred when the children were between the ages of 7 and 11 years. The youngest reported patient with endarteritis was 4 years of age.[7] Although better medical management with antibiotics has reduced the mortality of endarteritis, the prevention of this serious complication is best accomplished by the surgical closure of the ductus before the patient reaches the age of 5 years, since infection rarely occurs prior to this time.

Pulmonary arterial hypertension associated with patency of the ductus arteriosus has been observed in patients of all ages. Dammann and Ferencz [8] have shown that the extremely high pulmonary arterial pressures may be well tolerated by young individuals but that the disease is a progressive one and ultimately leads to the premature death of the patient, with myocardial decompensation and/or reversal of blood flow through the ductus. Ander-

son [9] has carefully studied 10 children with reversed flow and concluded that the reversal of flow in the ductus does not always represent the end-result of prolonged elevated pressure but may exist even in early infancy. Fortunately, young individuals with severe pulmonary hypertension tolerate closure of their shunt much better than do older children or adults.[10] In a selected series of patients with proved pulmonary hypertension (table 2) the mortality was 0 in 22 infants under 2 years of age and 10.5% in 19 younger children between the ages of 2 and 5, as compared with 26.7% in 15 patients between 5 and 16 years of age. These statistically significant differences in the operative risk are presumably due to the fact that the myocardial reserve of the patients is excellent and suggest that the pulmonary vascular resistance has not become fixed in the younger patients.

The pulmonary vascular degenerative changes are of two types. The first and most commonly encountered include those which are confined to the smaller pulmonary arterial vessels initially and include hypertrophy of the media and proliferation of the intimal layer. Medial hypertrophy of the pulmonary arteries is present in the normal human fetus and in the presence of an open ductus may persist into early infancy.[11] When the ductal shunt either closes normally or is obliterated surgically, hypertrophy of the medial layer apparently regresses and the vascular resistance presumably returns to normal. However, if the shunt remains open the pulmonary vasculature is subjected to prolonged increases in flow, pulse, and pressure, and the intimal proliferation progresses to sclerosis and thrombosis and eventual obliteration of the lumen, with concomitant increase in pulmonary vascular resistance, which ultimately becomes fixed and irreversible.[9]

The second but less common vascular degenerative change involves the ductus itself, the pulmonary artery, or the adjacent aorta. Lindert and Correll [12] collected 29 patients with aneurysm of these major vascular channels, the youngest of whom was over 5 years of age. Two of these patients died after a rupture of the aneurysm at 5 and 12 years of age. Holman [6] encountered one patient, 11 years of age, with an aneurysm of the ductus and another 14 years of age with a pulmonary arterial aneurysm. The youngest patient with aneurysm whom we have encountered in our review is one reported by Lyon and Kaplan [13]—an infant 27 days of age who died after thrombosis of a ductal aneurysm, and this condition was complicated by renal arterial thrombosis.

Disadvantages of Early Operation.—The disadvantages of early operation appear to be relatively negligible in the face of all of the evidence previously presented. Obviously, facilities and personnel capable of caring for infants and younger children must be utilized and fortunately are now widely available. Emotional problems are commonly encountered in children between 2 and 4 years of age, but in general can be dealt with judiciously by careful preparation of the family and the child prior to his admission to the hospital and by concern for his mental as well as physical requirements while he is incapacitated in this strange environment.

Conclusions

Surgical closure of a patent ductus arteriosus should be carried out on any child who shows symptoms as early as the diagnosis is established and in asymptomatic patients before they reach the age of 5 years. The operative morbidity and mortality in infants and younger children, as far as we can determine, is no greater than that experienced in older children. Failure to eradicate this lesion in early life may expose the infant with symptoms to progressive myocardial decompensation and the young child to the needless threat of cardiorespiratory disability, growth failure which may not be entirely reversible, and to such additional serious complications as endarteritis, irreversible pulmonary hypertension, and degenerative disease of the major and minor pulmonary vessels.

TABLE 2.—*Cases of Patent Ductus Arteriosus Selected Because of Proved Pulmonary Hypertension*

References	Age, Yr.* 2 Cases, No.	2 Deaths, No.	5 Cases, No.	5 Deaths, No.	5-16 Cases, No.	5-16 Deaths, No.
Damman, J. F., and Sell, C. G. R.: Circulation **6**:110, 1952	3	0	11	1	4	1
Ziegler[2]	6	0	2	0	...	...
Adams and others[3]	4	0	...	...	...	...
Ellis, F. F., and others J. Thoracic Surg. **31**:268, 1956	3	0	1	0	6†	1†
Anderson and others[9]	1†	0	1†	1†	1†	1†
Hay, J. D., and Ward, O. C.: Arch. Dis. Childhood **31**: 279, 1956	1	0	3	0	3†	1†
Clatworthy and McDonald, 1957	4	0	1	0	1	0
Totals	22	0	19	2	15	4

* At 2 years the mortality was 0, at 2 to 5 years 10.5%, and at 5 to 16 years 26.7%. The over-all mortality of the 56 patients was 10.7%.
† No. with reversal of flow.

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11. Civin, H. W., and Edwards, J. E.: Postnatal Structural Changes in Intrapulmonary Arteries and Arterioles, A. M. A. Arch. Path. **51:**192-200 (Feb.) 1951.

12. Lindert, M. C. F., and Correll, H. L.: Rupture of Pulmonary Aneurysm Accompanying Patent Ductus Arteriosus: Occurrence in 67 Year Old Woman, J. A. M. A. **143:**888-891 (July 8) 1950.

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SYMPATHY AND EMPATHY

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The person able to determine his emotional boundaries, that is, where he leaves off and where someone else begins, and not indulge in the other's emotional problems, functions more usefully, happily, and gracefully. It appears that one of the most difficult tasks put upon man is the reflective (not reflexive) commitment of oneself to another's problem, while each maintains his own identity. It is a state to which those in the interviewing professions should aspire. Though this is a proposition well known to psychology and psychiatry, it is rarely if ever considered in schools at any level. It follows that if we acquire this important talent by learning, we learn it later than we should. It ought to be possible to bring people to reflective commitment earlier and more gracefully than heretofore has been the case. It is likely that, if one has been strongly conditioned in youth to direction by the feelings of others (outer-directed is Riesman's term for it), this will later become almost a reflex. An emotional discharge by another then becomes a challenge. The ways in which one person may react to another are infinite; there is a spectrum of these reactions. In these exchanges it is quite unusual to witness reflective commitment and behavior predicated rather completely on what is happening now. Yet to the extent that this does not operate we are not free, an uneasy state of affairs to be sure. Old and established patterns much too often interfere with current functioning.

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The act or capacity of entering into or sharing the feelings of another is known as sympathy. Empathy, on the other hand, not only is an identification of sorts but also connotes an awareness of one's separateness from the observed. One of the most difficult tasks put upon man is reflective commitment to another's problem while maintaining his own identity. The ways in which one person may react to another are infinite. A subtle and significant feature of a happy medical practice is to remain unencumbered by the patient's problem.

> Thus conscience does make cowards of us all;
> And thus the native hue of resolution
> Is sicklied o'er with the pale cast of thought,
> And enterprises of great pith and moment
> With this regard their currents turn awry,
> And lose the name of action.
>
> Hamlet III. i. 56

To psychiatrists this is elementary; when a person has not matured emotionally, stimuli often evoke unrealistic behavioral patterns. People repeat themselves endlessly as though they had been hypnotized at some tender age and told that henceforth this is the way it was to be. The basic behavior of a person is largely unchanging, barring catastrophe or another moving emotional experience.

This repetition presents in various guises which remove the phenomenon from the realm of the obvious. It has been said of a person so hampered that "he has been 'taken in' so to speak by what he has taken in." [1]

Medical students and physicians do not escape this blight; behavior in others is apt to draw them into activity which they neither originated nor had any intention of entering into. The possibilities are varied and infinite, limited only by the energy that is available; waning energy may be a factor in the amelioration of such participation as we grow older. Physicians are doubly burdened when they are unable to unravel the meaning of such behavior in others, since so much that is constructive in therapy depends upon its recognition. It usually has not been possible for teachers to assist students toward enlightenment in this area. Indeed it is unlikely that most teachers, at least in schools of medicine, would consider this their function or responsibility. Whatever the case, I will point to some areas wherein impasses frequently develop in an interviewing profession such as medicine.

Many teachers of medicine advise the sympathetic approach; one cannot fully appreciate the problems of others, it has been said, unless he can put himself in another's place. We ought to consider exactly what we mean by this sympathy. On casual glance, sympathy would seem to be a quality devoutly to be wished for in the practice of medicine. Certainly most of us entered our profession with some such thinking; the sympathetic physician has been portrayed with persistence through the ages. As is often the case, the judicious use of a good dictionary may give us a hint as to what may be the matter with one or another cherished belief. If we thoughtfully examine the definition of the word sympathy, we find that it refers to an affinity, association, or relationship so that whatever affects one, similarly affects the other. The act or capacity of entering into or sharing the feelings of another is known as sympathy. Without crowding the definition we may say that this describes exactly what occurs in far too many human relationships, including the practice of medicine. I want to submit that entering into the feelings of another and becoming similarly affected may not be the constructive method that it has been supposed. There are so many examples of this affinity that it is difficult to know which to cite; the patient demands subtly or crudely and the physician either falls in with the demand or becomes annoyed; the patient prefers another medical advisor and the physician is hurt; or the patient becomes glad, mad, or sad or even amorous and the physician follows suit, and so on ad infinitum. It would seem as if the one affects the other similarly to his own feelings, surely restricting movement in him who is supposed to be acting maturely, unhamperedly, and realistically according to what is transpiring in the here and now. The doctor then "feeds back" problems as complex if not more so than those his patient brought to him, and energy is invested where it is wasted. We should become aware of the subtle deterioration of our usefulness in such situations. It is no longer the best medicine to proceed blindly motivated by humaneness; there has been developed a better way. Action motivated by conscious awareness is one of the main goals of today's psychiatrist.

The student of medicine rarely has the opportunity to learn about the great advantages that accrue to maintaining one's own personality in any emotional climate. The patient should be allowed his own problems without a need on the part of the physician to partake of them. This is the attitude best encompassed by the psychological term, empathy. The term empathy is thought to have originated with the German psychologist, Theodore Lipps, in the word einfühlung. Like many foreign conglomerates, einfühlung is difficult of translation. Einfühlung connotes the emotional appreciation of another's feelings, as does sympathy. Einfühlung, or empathy as we say, is an entrance into the feelings of another person or of a thing or concept; one may feel oneself into things contemplated or persons observed. This "in-feeling," or better "feeling-into," depends a good deal on the richness of one's own experience; it has to do with the matured use of the self. It is not only an identification of sorts, but unlike the implications of sympathy it is an awareness of one's separateness from the observed. One has had one's own feelings and relationships and has worked at the understanding of them, and they will be useful in understanding those feelings and relationships of others. Appreciation of another's feelings and problems is quite different from joining in them, and in so doing, complicating them beyond resolving. Empathetic understanding allows a better opportunity of defining what is transpiring and what the behavior of another signifies. It is hardly possible to overstate the importance of the uses of empathy in the practice of medicine.

What has been said so far may appear to give license to reticence in engaging the patient's main problems and to a passive or indifferent or lazy attitude of withdrawal on the part of the physician. This is about as far as it would be possible to get from the correct interpretation. Rather, the goal is to allow the physician the maximum freedom of movement so that he may act for the greatest benefit of the patient. One of the very greatest assets in the physician's possession is freedom of movement, and this may pertain only if the physician remains apart from the enervating morass of the patient's problems, viewing them detachedly yet

interestedly. It might be said quite simply that one cannot become interested in them short of being interested, a state that only the very greatest doctors achieve consistently. But we cannot hope to be of maximum help to the patient if we become subjective about the trouble and, therefore, partake of it. This is the main reason why the physician does not treat his own family.

I now want to turn to a few examples. We all know patients who constantly pick at us, in the provocative fashion of a youngster who is itching for a licking. They probe for the "soft spots"; usually they are burdened and uneasy people. By implication or even by direction they indicate that the physician does not know his business, or at the very least that he is doing them no good. Obviously we must be on firm ground in dealing with these persons as with all patients; one can never operate from a base of inadequate knowledge and expect to function as a first-rate physician. The basis of security in this regard is the thorough examination, for which there is absolutely no substitute. But indifferent technique or lack of knowledge is not the problem under consideration here. More often the physician is unable to withstand the patient's provocations mainly because of his own unmastered conflicts. He mistakes the patient's problem as his own; he picks up the emotional challenge and finds himself acting in a fashion suggested by the conduct of the patient. Clearly then he is being outer-directed.

Perhaps one of the most obvious examples of this outer-direction is the conduct of many physicians in their dealings with persons with dependency problems. These persons, in their contact with authority, repeat their unmastered emotional problems in such a way as frequently enough stirs the doctor to thinly disguised and even overt hostility. This destructive approach—of both participants I might say—is seen too often when the patient is receiving compensation for illness, and particularly compensation from public funds. Patients are hardly aware of the danger inherent in this position, or I do not believe they would cultivate it as often as they do.[2] Here the doctor is involved sympathetically; there is an affinity, association, or relationship with the patient, so that whatever affects one (the patient) similarly affects the other (the physician). This affinity impedes effectiveness, and the physician then proceeds haltingly and usually is blocked from performing the work he should be doing. Most physicians would rationalize this behavior as moral, perhaps noting that they reserve a full measure only for the deserving. As Cervantes said, it is the hardest job in the world to know oneself. With a bit of good-humored self-examination, it is readily understood that everyone has quite legitimately a longing to be taken care of; this is elemental in protoplasm. The dependent state was originally the privilege of all of us and no one of us budged from it with grace. There is ever the pull to return to the "good old days," and who has not experienced these nostalgic longings? Though we are prone to deny it, people who receive compensation for illness poorly understood —as an example, the neuroses—arouse in us an envy of sorts. When the reward is obtained from the "public trough"—some indication of piggishness—we are touched to the quick. This represents a kind of nirvana, a state we have longed for since we were too rudely removed from it, an unconscious longing to be sure, but more moving by reason thereof. So we transcend our medical competence to judge these sick people, and the more we judge the more we may be judged, since the emotional state which we deride with such vigor is that for which we long. As Shakespeare put it: "The lady doth protest too much, methinks."

Szasz[3] has published an interesting treatise concerning the physician's concept of malingering which bears on our problem. There is an old saying taken from Spinoza, as I remember, to the effect that Paul's idea of Peter tells us more about Paul than about Peter. A diagnosis of malingering expresses nothing so much as the physician's moral condemnation of the patient, and it tells us as much, if not more, about the physician than it does about the patient. With it the physician becomes dragooned into the role of an umpire; then it becomes his duty to see that no one cheats. Obviously medical training is not intended to make one expert as an umpire; perhaps the least that may be said against a diagnosis of "malingering" is that it draws the doctor away from his competence. The inferences are clear; one cannot allow oneself to be drawn sympathetically into activity that intellect ought to have warned is not within the purview of medical expertness. It should be obvious that patients who have been called malingerers are sick people, and it is our duty to find out why and what might be done toward remedy, and nothing more.

The temptation to transcend the boundaries of competence is a continuing one to men of medicine. If there were time it would be interesting to try to determine why this is so. Currently the need for authorities is very great indeed; the physician may find his opinion being sought in practically any problem that besets a human being. We are reminded about the old family doctor who—sainted and enshrined by death and distance—had his opinion asked in such things as investments, politics, and all sorts and conditions of behavior. The wise physician guards against any anachronism, and particularly this continuing temptation which may represent nothing more than the patient's attempt to cast him in the role of the all-giving father; a

role than which, although flattering, there is none more difficult in the world to maintain with consistency.

In this regard I am reminded of the many legalisms that somehow have been extended into medicine, for example, the terms insanity, per-cent-disability, and the irresistible impulse (I am taken with Justice Brandeis' remark that the irresistible is often only that which is not resisted). It is as though others, surveying the field of medicine and finding it not entirely to their liking, decided that the game was going to be played on different terms and then projected regulations with which they felt more at ease. The physician who plays the game away from his home base, away from his own unique competence, is in trouble. The best antidote for this temptation is self-examination, with attention to the concepts of sympathy and empathy as they have been developed here.

A group of patients who test our powers to act as an independent and inner-directed unit are those with emotional illnesses and particularly those whose problems are subtle and disguised, as may be the case in some conversion states and in masked depressions. So, too, with any complex illness where the diagnosis is difficult, and particularly when a deal of continuing pain is involved. These patients unmask our emotional inadequacy no less than the compensation cases. Knowledge is never complete, and those physicians in the thick of it must always handle a modicum of insoluble problems. This is no threat to those who have matured to the point of admitting to themselves that there are some things they can't know, even after thorough study. Kant's definition of faith applies here: "Again and again it is necessary to take a decision on the basis of knowledge sufficient for action but insufficient to satisfy the intellect." Not to know is a threat to a hampered personality, as it is to admit that there may be others whose competence extends into realms where he himself is not particularly interested. To obstruct treatment for a person who functions poorly for any cause, is surely to be "sucked in" and immobilized by the patient's problem. This is sympathizing rather than empathizing, an affinity or relationship so that whatever affects one, similarly affects the other.

Most of these people are in need of a steadfast and ongoing relationship, although some of them are even more in need of a thorough physical examination and a proper diagnosis. The physician may not be in a position to afford a continuing relationship to such persons for any of a number of reasons; frequently he hasn't the time to devote to it that they require. However, he may not be aware of his fear of it; when his tokens of relationship—namely pills and palaver—run out, he is in a sense bankrupt. He has no faith in relationship therapy, I suspect mainly because he does not know how to maintain his integrity in it. I don't mean this in any moral sense; I mean integrity from the standpoint of an independently functioning, secure, innerly directed, and well-integrated, singular unit.

The patient presumes him to be an expert and presents himself for treatment. The physician falls in with the patient's feeling; he sympathizes with the patient to the extent that he agrees that he is such an expert as the patient decrees him to be. He then pronounces him to have no illness with the usual phrasing: "There's nothing the matter with you." Into such travesties can our sympathies lead us! An empathetic physician might well say: "I know or I will find out about the trouble that you describe and I will work with you concerning it," or "I will send you to someone who does this type of work."

Another problem in this category is the pain sometimes suffered because of the resistance to giving analgesic drugs oftener than every two to four hours or so, and in no more than the usual dose. This applies particularly to patients who suffer from a fatal illness. I can make nothing of this problem unless it be another example in the realm that I have been discussing. Obviously addiction is not a consideration in this regard, certainly expense is not, and there is no danger of euthanasia, parenthetically a procedure in which I have no faith. I cannot see how the clock—that is, the movement of the earth on its axis—can have anything to do with the care of persons dying with excruciating pain. The main problem is to keep such people as comfortable as it is within our province to do, and besides giving of oneself this involves the proper use of more than the usual doses of potent analgesics in addition to nursing care and to comforting the family. If we are being subtly hampered in this endeavor it behooves us to find out why.

There is a concept of purification by suffering. But in our culture this punishment usually has been reserved for the criminal. One may presume that everyone is guilty, as some do, but this is an uneasy base from which to practice medicine, since once again this is beyond the province of our competence. It seems likely that here again we have become enmeshed by feelings of which we are unaware, and particularly those having to do with dependency. In an ongoing relationship it is difficult to be constantly gratifying the dependency feelings of others without garnering something in the way of emotional supplies in return. Perhaps this is where we fail, when we do, in the handling of chronic disease. Everyone finds it difficult to constantly give of his substance without receiving in return. The usual method to get around this has

been to file these people away from the stream of medical consciousness; up until recently most hospitals for the chronically ill were miles away from medical centers. There are, of course, many other reasons. But nothing but good can accrue to becoming aware of our own feelings as regards problems such as these. The best that derives therefrom is the freedom to act realistically and according to the current happenings.

A subtle and significant feature of a happy medical practice is to remain unencumbered by the patient's problem. Among others to point this up, particularly as far as fear is concerned, has been Wilmer [4] in his work with psychotic patients. Noting the experience of certain English psychiatric institutions where the staff expect the patients to control their own aggressive impulses, he operated a therapeutic community in a ward where all patients were free to move about and were expected to attend daily meetings. These meetings were followed by a staff conference. Both the staff's and patients' anxieties and interpersonal relationships were kept under constant scrutiny and study. An examination of the personal fears of physicians and other ward personnel was paramount in the scheme. A ward previously disturbed was thereby changed into a ward without restraint, the use of parenteral sedation was eliminated, and the amount of oral sedation was greatly diminished. It is not only on psychiatric wards that too much chemical and physical restraint has been used; there seems to have gotten around the idea that the quieter patient is the "good" patient. Restraints of all sorts and tubes from all orifices have become the order of the day. Without doubt this has something to do with the paucity of hospital personnel, but also there is some misunderstanding of their own motivations by that personnel.

These illustrations should suffice to point up the constructive value of empathy and the sometimes disorganizing effect of sympathy. Obviously it requires more than an understanding of the definition of words to become the good physician. But it helps to know even this much and a start must be made somewhere. The ability to be empathetic depends largely on the richness of one's own emotional experiences. These experiences are the basis of inner perception—intuition, as it is sometimes termed—the ability to understand one's own feelings and relationships, and by reason thereof, those of others. There is no substitute for knowing, and there is no knowing so useful as the knowledge of oneself. While this is meant in its broadest sense, the most important aspect of this knowing is the relaxed and confident use of one's own feelings. In this vein it is worth remarking how useful may be the symptoms that one has personally experienced in the handling of those of his patients. I have sometimes caught myself wondering if it might not be useful for physicians, nurses, and other hospital and clinic personnel to be ill periodically, to add to their understanding of the problems of patients.

In our culture we operate mainly from an intellectual base. In most circles knowing is still considered to be a conscious phenomenon, entirely dominated by intellect. We all know how we need to go to the books with great frequency in youth. Some of us never learn to trust our feelings or experience in dealing with problems as they arise, and there then must always be an authority outside oneself. This, at least in a degree, must reflect the conditioning that one has been exposed to in childhood.

In any case I consider it helpful to know intellectually the difference between sympathy and empathy and some of the implications thereof. Just this much may save the physician from acting in a manner suggesting that he himself imposed the disease on his patient and, while it should never lift him in any sense above the misery and suffering, it may allow him a certain freedom to act for the patient's greatest good. The ultimate test of any medical endeavor is what it does for the patient. The doctor proceeding bravely and courageously, to say nothing of good-humoredly, continuing to learn about himself and his own problems will be good for the patient.

Truth is within ourselves; it takes no rise
From outward things, whate'er you may believe.
There is an inmost centre in us all,
Where truth abides in fullness; and around,
Wall within wall, the gross flesh hems it in,
This perfect, clear perception—which is truth.
A baffling and perverting carnal mesh
Binds it, and makes all error: and, to KNOW,
Rather consists in opening out a way
Whence the imprisoned splendor may dart forth,
Than in effecting entry for the light
Supposed to be without.

Paracelsus—Robert Browning

3231 Burnet Ave. (29).

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CLINICAL NOTES

A SIMPLE TEST FOR MYOHEMOGLOBINURIA (MYOGLOBINURIA)

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and
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Like other rare diseases, myohemoglobinuria [1] (myoglobinuria) is believed to occur more often than the sparse number of reported cases (about 35) would indicate. Even when the diagnosis of myohemoglobinuria is entertained, it is difficult to distinguish between myohemoglobinuria and hemoglobinuria, a much more frequent condition. This differentiation until recently has required the use of a highly precise and carefully calibrated spectrophotometer usually found only in research laboratories. Even with such an instrument, and with both pure myohemoglobin (myoglobin) and hemoglobin saturated with carbon monoxide available for control determinations, differentiation is difficult since it depends on small differences in the position of spectral bands.[2] It has recently been suggested that, with a fluorescent lamp as a source of light, the hand spectroscope may be used to identify myohemoglobin.[3] Also, in one case, paper electrophoresis has been used to diagnose myohemoglobinuria.[4] A simple chemical method for differentiating between myohemoglobinuria and hemoglobinuria is presented below.

Technique

First, the abnormal pigment, which is red in freshly voided urine (myohemoglobin) but turns brown or black on standing (met-myohemoglobin), must be demonstrated to be a protein. Furthermore, the presence of other abnormal pigments of nonprotein nature must be ruled out. To 1 ml. of urine add 3 ml. of 3% sulfosalicylic acid.[5] Mix and filter or centrifuge. If the pigment is precipitated, it is a protein. If the filtrate or centrifugate is the normal color of urine, no abnormal nonprotein pigment is present. (The classical heat-and-acetic-acid test does not precipitate either myohemoglobin or hemoglobin.)

Second, to 5 ml. of urine add 2.8 Gm. of ammonium sulfate and dissolve by mixing. This brings the urine to 80% saturation. The urine is then filtered or centrifuged. If the filtrate or centrifugate displays the abnormal color, myohemoglobin (met-myohemoglobin) is present. If only the normal color of urine is visible, the precipitated pigment is hemoglobin. This test is applicable both to freshly voided urine and to properly preserved urine. For preservation, the urine should be adjusted to pH 7.0 to 7.5 with dilute sodium hydroxide and then refrigerated. Urine preserved in this manner for as long as two months was still capable of giving a positive test for myohemoglobin, despite a moderate degree of bacterial contamination.

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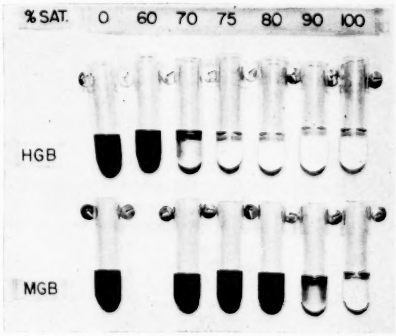
Comment

This test has been successfully applied in two cases of idiopathic paroxysmal myohemoglobinuria. In one case the urine was acid and in the other it was alkaline. The presence of myohemoglobin was confirmed by spectrophotometry and paper electrophoresis in both cases. In five cases of hemoglobinuria the test correctly indicated the presence of hemoglobin. The difference is solubility on which the test is based has been applied for many years to the removal of hemoglobin during the preparation of myohemoglobin from muscle.[6] At 80% saturation with ammonium sulfate, hemo-



Filtrates of normal urine to which human hemoglobin was added (upper row of tubes) and of urine from a patient with myohemoglobinuria (lower row). Increasing amounts of ammonium sulfate added before filtration to give percentage of saturation indicated above tubes. Faint traces of hemoglobin still present at 75% saturation, not apparent in photograph.

globin is completely precipitated from solution, along with denatured myohemoglobin, but only minor amounts of undenatured myohemoglobin are precipitated (see figure). At 100% saturation, myohemoglobin is completely precipitated, together with significant amounts of normal urinary pigments.

Only when the abnormal pigment has been shown by the sulfosalicylic acid test to be protein is this test applicable. Demonstration that the pigment is a protein rules out porphyrinuria, alkaptonuria, and drugs or dyes as causes of abnormally pigmented urine. The test described here is not only of use in confirming the diagnosis of myohemoglobinuria but may also help define more sharply the clinical entity march hemoglobinuria[7] or "exercise myohemoglobinuria."[8] Undoubtedly, many cases of exertional myohemoglobinuria have been classified as march hemoglobinuria,[9] apparently for want of a simple, readily available diagnostic test. All the clinical and laboratory criteria that may be used in differentiating between myohemoglobinuria and hemoglobinuria are listed in the table.

*Differentiation Between Idiopathic Myohemoglobinuria and Hemoglobinuria**

	Myohemoglobinuria	Hemoglobinuria
Clinical signs and symptoms	Painful, tender, swollen muscles with limitation of motion	Muscles normal
Appearance of serum.	Not hemolytic	Hemolytic
Serum bilirubin	Normal	Rises
Reticulocyte count	Normal	Rises
Spectral characteristics of urinary pigment:		
Nonoxygenated	Rapidly changes to met-form giving spectrum almost identical with that of met-hemoglobin	Does not usually change to met-form spontaneously
Oxygenated form	Maximum absorption peak at 582†	Maximum absorption peak at 577†
Carbon monoxide complex	Maximum absorption peak at 579	Maximum absorption peak at 570
Electrophoresis	Myohemoglobin (met-myohemoglobin) migrates at about half the speed of hemoglobin in barbital buffer pH 8.6	
Solubility in urine 80% saturated with ammonium sulfate	Myohemoglobin largely remains in solution	Hemoglobin completely precipitated

*Large differences in molecular weights and oxygen dissociation curves of myohemoglobin and hemoglobin might also be of value in their differentiation.

†Fluorescent lamp as source of light aids in differentiation-based on this spectral difference.[8]

Summary

A simple test can differentiate myohemoglobinuria from hemoglobinuria by means of 80% saturation of the urine with ammonium sulfate.

This study was aided by the Anna R. Wasserman Lowenberg Research Fund.

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INCREASED LINOLEATE CONTENT OF FOODS.—We know that the essential polyunsaturated fatty acid—linoleic acid—is assumed by many to play a major role in the diets known to lower the serum cholesterol. . . . A number of common foodstuffs can be modified so as to increase their content of linoleic acid appreciably without changing taste or appearance. Vegetable oil can be homogenized with skim milk to produce a palatable whole milk. Ice cream and certain cheeses can be made with vegetable oils rather than butterfat, and a spread resembling butter can be manufactured that is rich in linoleic acid. Chickens, if fed a diet rich in essential fatty acids, will produce eggs whose yolks contain a high proportion of polyunsaturated fatty acids. All these things are within our technical grasp—the point is, we still do not have a pattern of fatty acids that we can refer to as being optimal for human health.—T. B. Van Itallie, M.D., Nutritional Research in Atherosclerosis—A Progress Report, *Journal of the American Dietetic Association*, March, 1958.

INTESTINAL OBSTRUCTION DUE TO BISHYDROXYCOUMARIN POISONING

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The excellent results achieved by long-term therapy with anticoagulants in cases of coronary thrombosis and recurrent thrombophlebitis have been marred by the occasional severe toxic reaction. Hematuria, gastrointestinal bleeding, and hemoptysis are the most commonly encountered complications. Toxic manifestations of bishydroxycoumarin (Dicumarol) therapy producing acute abdominal

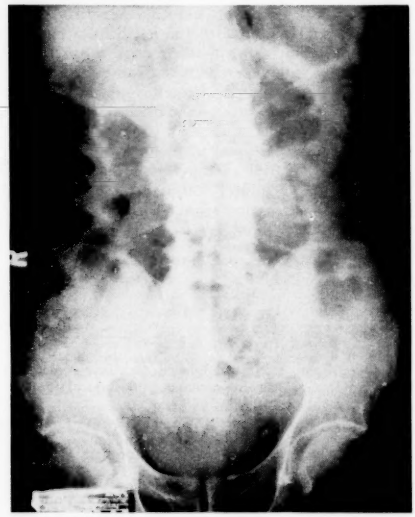

Fig. 1.—Roentgenogram of abdomen, with patient recumbent. Horseshoe loop of distended intestine in upper abdomen cannot be differentiated as to small or large intestine.

emergencies have been infrequently reported. Berman and Mainella,[1] in 1952, reported five cases of anticoagulant toxicity resulting in abdominal symptoms, in one of which the patient presented signs of intestinal obstruction. At operation a hemorrhagic infarct of the jejunum was found and resected. Mendelsohn and Iglauer,[2] in 1953, reported two cases of bishydroxycoumarin toxicity producing a picture of intestinal obstruction. Both patients had free blood on the peritoneal cavity; however, no obstruction was found.

From the surgical service of the Seaside Memorial Hospital.

The following case represents a rare instance of intestinal obstruction caused by overdosage of bishydroxycoumarin.

A 69-year-old man was admitted to Seaside Memorial Hospital for the third time on April 21, 1957, complaining of cramping abdominal pain and vomiting blood for three days. He had been well until Aug. 1, 1956, when he was hospitalized for thrombophlebitis of the left leg with a left pulmonary infarct. Bishydroxycoumarin therapy was started, and the patient was discharged, remaining on this therapy, on Aug. 14, 1956. He was readmitted to the hospital on Feb. 23, 1957, with pain and claudication of one month's duration in the right calf. Bilateral femoral arteriography showed obstruction of both superficial femoral arteries with poor peripheral run-off. After this hospitalization he was maintained on bishydroxycoumarin therapy on an outpatient basis. Control remained at a therapeutic level until four weeks before admission, when the patient failed to return for follow-up.

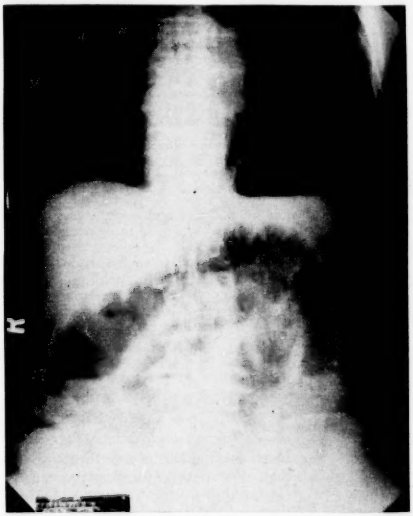

Fig. 2—Roentgenogram of abdomen, with patient standing. No fluid levels are seen in the intestine.

For the next four weeks the patient took as much of the drug as he felt he needed, sometimes as much as 200 mg. per day.

Physical examination on admission showed a pulse rate of 76 per minute, respiration rate 20 per minute, temperature 98.6 F (37 C), and blood pressure 110/80 mm. Hg. Eyes, ears, nose, and throat were not remarkable. There were wheezes, without rales, in both lungs. The abdomen was

distended and tense with shifting dullness. No peristalsis was heard. The laboratory examination showed a red blood cell count of 4,700,000 per cubic millimeter. The hemoglobin level was 13.6 Gm. per 100 cc. Urinalysis was normal. Prothrombin time was under 10%.

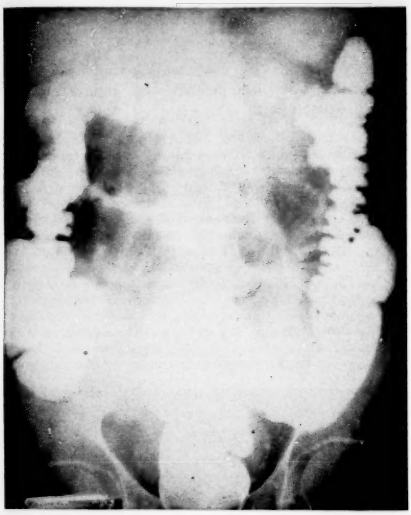

Fig. 3.—Roentgenogram of colon after barium enema. Distention of small intestine is consistent with mechanical obstruction.

During the next 24 hours the patient was given 150 mg. of vitamin K, oxide. He vomited blood on three occasions, approximately 300 cc. each time. On the second hospital day, chest and abdominal x-rays revealed pneumonitis at the base of the right lung and obstruction of the small intestine, although the possibility of an obstruction of the large intestine could not be completely excluded (fig. 1 and 2). A tentative diagnosis of intestinal obstruction was made, and surgical consultation was requested. A barium enema outlined a normal colon (fig. 3).

Blood transfusions were started, and the patient was taken to surgery at 8 p. m. At operation a moderate amount of free blood was present in the peritoneal cavity. The upper jejunum was markedly dilated. The obstruction was produced by massive hemorrhage into the wall of the jejunum approximately 6 in. in length. There were also other segments of the small intestine with areas of subserous hemorrhage. The involved segment of jejunum was resected, and intestinal continuity was restored by end-to-end anastomosis. The postoperative course was uneventful and the patient was discharged on the eighth postoperative day.

In a specimen consisting of a 20-cm. segment of small intestine, the entire wall was hemorrhagic and measured 10 mm. in thickness. The mesentery was hemorrhagic. Two centimeters of the proximal and distal end showed normal mucosal pattern. Dense hemorrhagic infiltrations were seen microscopically throughout the entire thickness of the intestinal wall.

Hemorrhagic infarcts of the small intestine producing intestinal obstruction have been reported infrequently. Spencer, Bateman, and Horn [3] collected 33 cases from the literature and added one of their own. Bishydroxycoumarin toxicity producing intestinal obstruction via a hemorrhagic infarct is an even more unusual phenomenon. It is doubtful that conservative therapy would result in resolution of a large infarct and, in the face of a true mechanical obstruction, would be extremely dangerous.

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DIAGNOSIS OF VIRUS INFECTIONS.—Immunologic and serologic studies offer the most practical approach to the diagnosis of virus infections. . . . Immunologic studies of diagnostic significance can be carried out only if blood is obtained in both the acute and convalescent phases of an infection. A single high titer may only reflect previous experience with a suspected virus and bear no relationship to the disease being studied; a minimum of a four-fold increase in antibody concentration is considered diagnostic. The serum should be obtained three to six weeks apart, collected under sterile precautions, and stored at 4° C. until studied. The main disadvantage of this method is that the etiology of an infection is not immediately apparent. . . . Serologic tests of value in the diagnosis of viral infections are complement fixation, agglutination, hemagglutinin-inhibition and neutralization. Complement-fixation has the greatest field of application. Hemagglutinin-inhibition and detection of neutralizing antibody are the next most useful; agglutination is employed least frequently.—Louis Weinstein, M.D., and Te-Wen Chang, M.D., The Diagnosis of Virus Infection, *The Medical Clinics of North America*, September, 1957.

THROMBOCYTOPENIA AND LEUKOPENIA ASSOCIATED WITH USE OF SULFAMETHOXYPYRIDAZINE

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and
William S. Norton II, M.D., New York

Sulfamethoxypyridazine (Kynex) has recently been introduced as a new antibacterial sulfonamide with good gastrointestinal absorption and prolonged action. It has been proposed for use both as a prophylactic agent and for the therapy of subacute or chronic infections where sulfonamides have previously been employed.[1] To date no reports of major toxic reactions to sulfamethoxypyridazine have been noted in the literature. It is the purpose of this report to present two cases of severe toxicity with predominantly hematological manifestations secondary to sulfamethoxypyridazine.

Report of Cases

CASE 1.—A 36-year-old housewife noted headache, heavy yellow postnasal drip, and fever on June 13, 1957. Two days later her private physician started therapy with sulfamethoxypyridazine, 0.5 Gm. twice a day. A total of 15 tablets were taken in seven and one-half days. On the eighth day the patient observed a "rash" and that evening vomited "coffee ground" material. The following day the rash was seen to consist of discrete small red spots which were not pruritic, and she observed blood in the urine. Ten days after the start of sulfamethoxypyridazine therapy the patient noted vaginal bleeding, and the following day she vomited blood and had a series of bowel movements containing fresh blood. History revealed that the patient had taken an unknown sulfonamide some years previously for a respiratory infection without untoward reaction.

Physical examination when the patient entered the hospital on June 25 revealed an afebrile woman with a blood pressure of 96/60 mm. Hg. There was a generalized purpuric rash, most marked on the legs, lower arms, and axillary folds. The Rumpel-Leede test was positive. The gums were pale, and a few purpuric spots were seen on the hard and soft palates. The pharynx was otherwise normal. The nose was moderately congested with a clear mucoid discharge. The liver was palpable 2 cm. below the right costal margin and was elastic but not tender. The spleen was not palpable and there was no lymphadenopathy. A profuse, bloody vaginal discharge was evident, and bloody feces were found in the rectum. Serial blood cell counts are recorded in the table. The day after admission a peripheral blood smear showed moderate hypochromia and basophilic stippling. The reticulocyte count was 6.5% and the prothrombin time was normal.

The markedly reduced number of platelets seen on the peripheral blood smear supported the initial clinical impression of a thrombocytopenic syndrome. This was confirmed by the platelet count of 8,000 per cubic millimeter on the following day. The anemia was felt to result from blood loss. The patient was given ACTH gel, 40 units intramuscularly, daily for three days and prednisone, 10 mg. four times daily, for five doses and then every eight hours through the remaining five days of her hospitalization. In addition she was given 1 Gm. of ascorbic acid, 50 mg. of rutin, and 1.2 Gm. of ferrous sulfate daily until discharge.

From the Department of Medicine, St. Luke's Hospital.

The patient remained afebrile, and no new cutaneous bleeding was observed after the first hospital day. The vaginal bleeding ceased by the third day, at which time the Rumpel-Leede test was negative. The platelet count rose rapidly to normal. The liver remained as on admission. After one week of hospitalization the patient was discharged. A maintenance dose of 10 mg. of prednisone was given daily for five days. A complete blood cell count performed on Aug. 5, 1957, revealed a hemoglobin level of 12 Gm. per 100 cc., a red blood cell count of 4,260,000 per cubic millimeter, and a white blood cell count of 7,700 per cubic millimeter, with a normal differential. The platelet count was 220,000 per cubic millimeter.

CASE 2.—A 64-year-old male had suffered from chronic benign prostatic hypertrophy and chronic nonspecific prostatitis since April, 1952. He was followed at six-month intervals. On April 6, 1957, he complained of some recurrence of perineal discomfort. The prostatic expression at that time revealed pus clumps. The patient was given 3 Gm. of sulfisoxazole (Gantrisin) per day for two days. When he was seen on June 8, 1957, his symptoms had increased and, in addition to an increase in residual urine, the pus clumps were increased in the prostatic expression. The patient was given sulfamethoxypyridazine, 0.5 Gm. every six hours for four doses, and then was instructed to take 0.5 Gm. daily. Four weeks later pus was still present in the prostatic expression, and the dose of sulfamethoxypyridazine was increased to 0.5 Gm. twice a day. On the 30th day of sulfonamide therapy, a complete blood cell count revealed a hemoglobin level of 12.5 Gm. per 100 cc., a red blood cell count of 4,100,000 per cubic millimeter, and a white blood cell count of 5,150, with a normal differential. On smear the red blood cells and white blood cells appeared normal. On July 20, 42 days after the start of sulfamethoxypyridazine therapy, the patient developed malaise and stopped medication but resumed it again on the following day. The next day, the patient experienced chills, fever, and back pain relieved by aspirin. Two days later the metacarpophalangeal joints of the thumbs became acutely painful, as did the right shoulder. At the same time a rash consisting of "tiny red spots" was observed in each axilla and a "red blush" developed over the upper trunk. The temperature rose to 103 F (39.4 C).

Physical examination on admission revealed an acutely ill, elderly male with a temperature of 104 F (40 C), blood pressure of 166/100 mm. Hg, and a pulse rate of 120. Over the upper trunk there was a diffuse, red, macular rash, and numerous petechiae were observed in each axilla and in the groin. A firm nontender liver was palpated 3 fingerbreadths below the right costal margin. The spleen was felt 1 fingerbreadth below the left costal margin and was soft and nontender. There was acute tenderness over the metacarpophalangeal joints of both thumbs and on motion of the right shoulder. The Rumpel-Leede test was markedly positive.

Urinalysis on admission revealed a specific gravity of 1.015, acid reaction, and no albumin, sugar, or bile; the microscopic examination was negative, including a search for abnormal crystals. Three subsequent urinalyses were normal. The serial blood cell counts are recorded in the table. The bone marrow aspirate two days after admission

revealed mild granulopoietic hyperplasia with prominence of immature forms and a decrease in erythropoiesis. Megakaryocytes appeared normal. Marrow examination six days later was normal. Blood chemical findings on admission were as follows: blood urea nitrogen, 11.9 mg. per 100 cc.; albumin, 3.7 mg. per 100 cc.; globulin, 2.5 mg. per 100 cc.; serum glutamic oxalacetic transaminase, 74 units; alkaline phosphatase, 4.6 King-Armstrong units; acid phosphatase, 1.1 King-Armstrong units; bilirubin, 0.6 mg. per 100 cc.; sodium, 148 mEq. per liter; potassium, 3.6 mEq. per liter; chlorides, 107 mEq. per liter; and cephalin flocculation, 3+. The sulfobromophthalein (Bromsulfalein) test revealed 15% retention after 45 minutes. One week later the sulfobromophthalein retention was 6%; serum glutamic oxalacetic transaminase, 30 units; alkaline phosphatase, 5.2 King-Armstrong units; cephalin flocculation negative; and thymol turbidity 12.9 units. The serology was negative. Examination of a clotted peripheral blood specimen for L. E. cells was negative. X-rays revealed only osteoarthritic changes.

The markedly reduced number of platelets seen on the peripheral blood smear supported the initial clinical impression of a thrombocytopenic syndrome. This was confirmed by the platelet count of 46,000 per cubic millimeter on the following day. The presence of fever, arthritis, hepatosplenomegaly, and lymphadenopathy suggested serum sickness.

Serial Blood Cell Counts in Two Cases of Thrombocytopenia Associated with Use of Sulfamethoxypyridazine

Date	Hemoglobin, Gm./100 Cc.	Leukocytes, % Total/ Cu. Mm.	Polymorphonuclear Cells	Band Cells	Lymphocytes	Monocytes	Eosinophils	Basophils	Platelets/ Cu. Mm.
Case 1									
6/25	8.9	8,700	52	0	42	4	2	0	(Few on smear)
6/26	8.3	10,400	75	0	22	2	0	1	8,000
6/28	8.1	13,100	63	0	29	7	0	1	140,000
6/29	8.3	12,500	61	0	33	5	0	1	251,000
Case 2									
7/24	13.6	3,200	61	4	19	2	0	14	(Few on smear)
7/25	13.2	2,050	60	0	16	20	2	2	46,000
7/26	14.4	1,750	87	2	22	34	0	3	28,000
7/27	14.8	2,600	38	0	26	36	0	0	92,000
7/29	15.2	5,200	65	0	31	4	0	0	115,000
8/1	15.6	8,200	55	0	37	8	0	0	190,000
8/2	14.8	7,450	66	0	28	5	1	0	240,000

Prednisone, 10 mg. every six hours, was given starting on the day of admission. After four days, dosage was slowly decreased and the drug was withdrawn on the 10th hospital day. A single injection of 40 units of ACTH gel was given on each of the last two days of prednisone therapy. There was a prompt symptomatic response. The patient's temperature was 104 F on the first day and was normal by the third hospital day. No new cutaneous bleeding was observed after the first day. The platelet count reached normal levels on the 10th hospital day and the Rumpel-Leede test became negative 3 days later. Leukopenia was most marked three days after admission. The white blood cell count returned to normal on the sixth hospital day.

At the time of discharge, on the 12th day, the spleen had receded to 1 fingerbreadth below the left costal margin and the liver was only 1½ fingerbreadths below the right costal margin. The lymphadenopathy had regressed to one-half its previous proportions. One week later the spleen was no longer palpable. Follow-up examination has revealed no alteration in these findings.

Comment

Serious reactions after the use of sulfonamides have frequently been reported. The incidence of these toxic side-effects varies with the preparation used. A history of reaction to any sulfonamide makes a reaction to its subsequent use more likely and may sensitize the patient to other drugs of this group.[2] It is of interest that both of the reported patients had previously ingested a sulfonamide compound without untoward reaction.

The mechanism of drug-induced thrombocytopenia is generally thought to be an immunological reaction in which platelet agglutinins can frequently be demonstrated. Recovery is usually spontaneous on withdrawal of the offending medicament.[3] The use of steroids for bleeding secondary to thrombocytopenia appears well established. Their efficacy is believed to reflect an effect primarily upon capillary resistance although on occasion steroid therapy does cause an increase in platelet count or a fall in platelet agglutinins.[4]

Although steroids were not used in the reported cases in a specific effort to influence the white blood cell count, it is worthy of note that these compounds are considered of value in the treatment of toxic granulocytopenia—particularly where leukocyte agglutinins can be demonstrated.[5] Development of serum sickness after use of sulfonamides has been emphasized by Longcope.[6] The time interval between first contact and the development of the clinical state in the second case was 45 days—somewhat longer than usually reported.

Summary

Two cases of thrombocytopenia were associated with the use of sulfamethoxypyridazine. In the second case leukopenia was also noted.

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MYOCARDIAL INFARCTION IN AN INFANT WITH TRANSPOSITION OF THE GREAT VESSELS

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In complete transposition of the great vessels, the aorta arises from the right ventricle and the pulmonary artery from the left ventricle. This congenital anomaly is incompatible with survival unless there is a septal defect which allows mixture of arterial and venous blood.

The case reported here is of particular interest because an electrocardiogram taken a few hours before death showed the pattern of an impending anterior myocardial infarction. This, as far as could be determined, has not been previously reported in a 7-week-old infant with complete transposition of the great vessels.

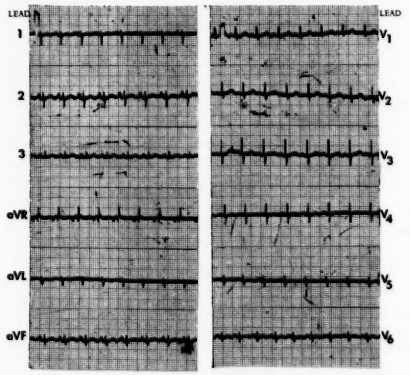

Fig. 1.—Electrocardiogram taken two days after birth. Findings are essentially within normal limits.

From the Department of Electrocardiography, St. Mary's Hospital.

Report of a Case

In a male infant who was born at St. Mary's Hospital on March 27, 1957, marked cyanosis appeared soon after birth. X-ray of the chest showed no evidence of pathology. An electrocardiogram taken two days after birth (fig. 1) was not definitely abnormal. A systolic murmur was heard over the precordium. The infant made fairly good progress and was dismissed from the hospital.

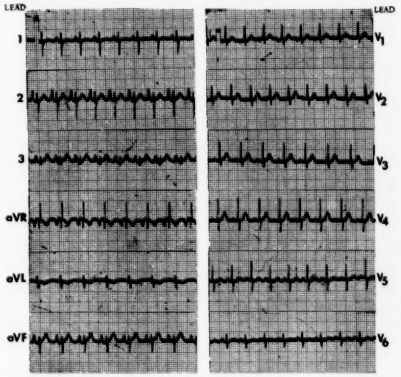

Fig. 2.—Electrocardiogram taken at age of 7 weeks. Tall, prominent P waves best seen in lead 2 indicate auricular hypertrophy. R wave in V_1 and aVR is much more prominent and S wave in lead 1 deeper, as compared to previous tracing (fig. 1). These findings indicate right ventricular hypertrophy.

The patient was readmitted on May 17, 1957, approximately 7 weeks old. There was marked dyspnea, cough, and cyanosis, and a systolic murmur was heard over the precordium. The x-ray findings were as follows: "Cardiac enlargement and liver enlargement with increased vascularity of the lung fields, probably representing some degree of congestive changes." An electrocardiogram (fig. 2) revealed

the following information: "The changes which have occurred since the last tracing was taken indicate considerable auricular and right ventricular hypertrophy." The patient was again dismissed from the hospital on May 21, 1957, only to be readmitted the following day. There was deep cyanosis, gasping respiration, and evidence of bronchopneumonia. A chest x-ray taken at that time showed enlarged cardiac silhouette and pulmonary congestion. An electrocardiogram (fig. 3) was obtained a few hours before death. The changes indicated an impending anterior myocardial infarction.

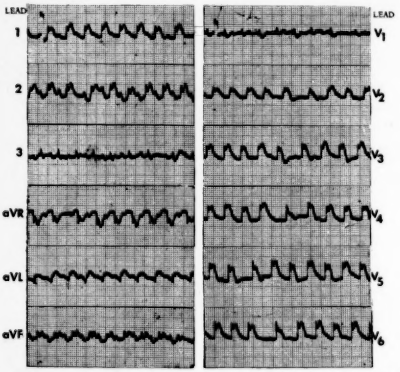

Fig. 3.—Electrocardiogram taken at the age of 7 weeks and a few hours before death. Marked ST segment elevations are apparent in Leads 1, 2, aVL, and most of the precordial leads. Q wave has developed in aVL. These findings indicate impending anterior myocardial infarction.

Autopsy Findings.—The heart was enlarged. The foramen ovale and duct arteriosus were patent. There were no defects of the interatrial and interventricular septums. There was transposition of the great vessels. The aorta arose from the right ventricle. The right ventricular myocardium measured 0.4 cm. in thickness. The valves were smooth and competent.

On microscopic examination a section from the anterior portion of the interventricular septum showed a few small focal areas of necrosis associated with interstitial hemorrhages. The endocardium showed moderate proliferative reaction and the presence of a few prominent nerve trunks. There was no inflammatory cellular exudate. The myocardial necroses were ischemic in origin.

Comment

Transposition of the great vessels is incompatible with survival unless there is a septal defect, most commonly a patent foramen ovale. In complete transposition, as in this case, the circuit from right ventricle to the transposed aorta and systemic circulation is virtually closed, as is the circuit from the left ventricle into the transposed pulmonary artery and lesser circulation. Admixture of blood is possible only through an associated shunt, in this case, a patent foramen ovale. With the failure of the left ventricle this shunt practically ceased. The coronary arteries arising from the transposed aorta received only venous blood, which in turn led to necrosis of the myocardium, presenting in the electrocardiogran a pattern of acute myocardial infarction.

Summary

An unusual case of myocardial infarction occurred in an infant 7 weeks old with transposition of the great vessels. Serial electrocardiograms were taken from the time of birth to the time of death. The congenital cardiac anomaly and the myocardial infarction were verified at autopsy. Complete transposition of the large vessels with the coronary arteries arising from the transposed aorta supplying mostly venous blood to the myocardium was the basic congenital anomaly in this case. Myocardial infarction in infants has been described by others, but always on the basis of congenital anomaly of the coronary vessels. This case, as far as could be determined, is the first in which myocardial infarction resulted as a direct result of transposition of the great vessels with the coronary arteries originating in the transposed aorta. The diagnosis of myocardial infarction was clearly established before death by the electrocardiogram.

ANTIBIOTICS AND TUBAL PREGNANCY.—Krohn, Beacham, Johnson, Greenhill, and others feel that there is an increasing incidence of tubal pregnancy caused by the common usage of antibiotics in treating salpingitis. Tubal patency is being maintained in patients who formerly would have had complete tubal occlusion. The presence of a patent tubal lumen does not mean that normal tubal physiology is maintained. The disturbance of the function of the tubal ciliary cells, decrease in peristaltic activity, and creation of more blind folds undoubtedly delay the migration of the fertilized egg and predispose to tubal nidation. Since these changes are more marked in the distal one third of the tube and since the "chronic" ectopic pregnancy usually occurs in the terminal portion of the tube, it seems reasonable to conclude that antibiotic therapy may predispose to the more chronic or obscure forms of ectopic gestation.—S. L. Parker Jr., M.D., and R. T. Parker, M.D., "Chronic" Ectopic Tubal Pregnancy, *American Journal of Obstetrics and Gynecology*, December, 1957.

COMPLETE INTRATHORACIC GOITER SIMULATING AN ANEURYSM OF THE ASCENDING AORTA

REPORT OF A CASE

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and
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Aberrant thyroid tissue is most commonly found in the thorax.[1] Many case reports have been published about aberrant thyroid tissue, whereas reports of complete intrathoracic goiters without visible cervical connections are rare. Many of the so-called complete intrathoracic goiters will be found to have some slight but definite connection within the neck.

DeCourcy and Price[2] reported finding three "complete" intrathoracic goiters in a series of 1,000 thyroid operations, all of which had some cervical connection. In 1947 Rives[3] reviewed the English and European literature for the years 1936-1946. He found only 14 cases of complete intrathoracic goiter. Of these, only two had no cervical connection. Ellis, Good, and Seybold[4] in 1957 reviewed reports of intrathoracic goiters removed at the Mayo Clinic and found 24 cases on file in which the tumor was removed by routes other than cervical. Only five of these were felt to have had no connection in the neck.

The problem of differentiation between various complete intrathoracic goiters and other thoracic lesions occasionally becomes extremely difficult because of conflicting results in diagnostic studies. The following case is presented to illustrate this difficulty.

A 39-year-old woman was admitted to the University Hospital on March 9, 1954, complaining of pain in her back which radiated to the right side of her chest. The history revealed that the patient had had an abdominal-perineal resection 10 years previously for rectal stricture secondary to lymphogranuloma venereum. Roentgenographic examination and fluoroscopy prior to hospitalization gave an impression of a small, saccular aneurysm of the ascending aorta. Physical examination revealed a well-nourished, well-developed, Negro female in no acute distress. The essential physical findings were as follows: The neck was supple with no adenopathy, and the thyroid was not enlarged. The trachea was questionably shifted to the left. There was no tracheal tug. There was some hoarseness to her voice; however, the vocal cords were normal. The chest, lungs, and heart were not unusual; no bruit or murmurs were heard. The abdomen was negative except for a colostomy in the left lower quadrant and a well-healed left paramedian incisional scar. Roentgenographic examination of the chest revealed a shadow which was thought to be a saccular aneurysm of the thoracic aorta at the junction of the ascending aorta and innominate artery, measuring 4 by 5 cm. (fig. 1 and 2). A retrograde aortogram was interpreted as "aneurysm of the ascending arch of the aorta beginning at the region of the innominate artery." On reexamination of the chest, including fluoroscopy and barium meal, there was again demonstrated the above density in the right mediastinum in the area of the ascending arch of the aorta. The Valsalva test was performed and, although the mass did not rise, it appeared wider and to pulsate, although the examiner could not tell whether the pulsations were expansile in type. A radioactive iodine survey suggested a substernal or mediastinal thyroid mass. A larger dose of radioactive iodine was given a few days later, and it was felt that the mass was thyroid tissue. The neck was explored through a collar incision. The lobes in the thyroid gland were identified. The gland appeared to be entirely normal; there was no evidence of substernal extension; and no definitive procedure was performed. Eight days later, a right thoracotomy was performed and a nodule measuring 4.5 by 3.5 by 3 cm. was found fixed to the anterior ascending aorta near the arch. There could not be demonstrated any type of connection, either fibrous or vascular, between this tumor and the neck. The tumor was dissected free from the aorta and excised without difficulty. The tumor bed was very vascular, but no large blood vessels were noted. The many small vessels supplying the tumor apparently arose directly from the aorta. Microscopic examination of the operative specimen revealed adenomatous thyroid tissue (fig. 3). The patient made an uneventful recovery and was discharged from the hospital on the ninth postoperative day. Two years later, radioactive iodine studies were reported as showing normally functioning cervical thyroid tissue without evidence of substernal extension. The patient stated that she had been asymptomatic since operation.

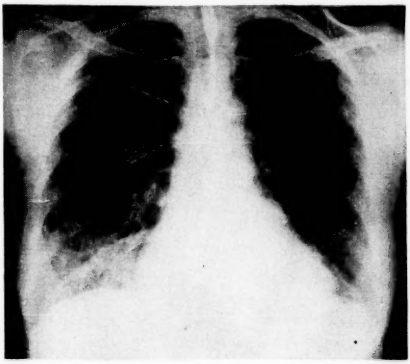

Fig. 1.—Posteroanterior chest x-ray demonstrating lesion at level of ascending aorta.

From the Department of Surgery, University of Maryland School of Medicine.

1958
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Comment

In an effort to study and consider this type of intrathoracic goiter comprehensively, a differentiation should be made between the three main categories of thyroid tissue: (1) true accessory thyroid glands derived directly from the main thyroid anlage during embryonic life; (2) metastatic thyroid tissue representing cellular masses that are disseminated to different parts of the body from an abnormally proliferating thyroid gland; (3) teratomoid thyroid tissue, perhaps springing from blastomeric material that was deranged or misplaced during the early states of embryonic life.[5]

Since the most common form of anomalous thyroid tissue is that located in the thorax, many classifications have been proposed. Rives [3] believes that there are two general groups: (1) aberrant mediastinal goiters and (2) substernal goiters. This author feels that aberrant mediastinal goiters include all those which have no connection with the thyroid gland proper. He believes that this type arises from aberrant thyroid tissue located within the thorax. Falor and co-workers [6] agree with this concept of origin but classify intrathoracic goiter on the basis of vascular supply: (1) primary intrathoracic goiter (intrathoracic origin of vascular pedicles); (2) secondary intrathoracic goiter (cervical origin of vascular pedicles).

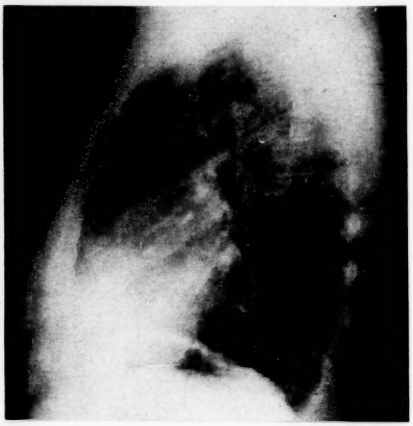

Fig. 2.—Right lateral chest x-ray demonstrating lesion at level of ascending aorta.

Johnston and Twente [7] hypothesized that all intrathoracic goiters arise from the cervical thyroid and receive their blood supply from the superior thyroid or from the inferior thyroid arteries. In support of this theory, many of the so-called complete intrathoracic goiters will be found to have some slight but definite connection with the neck. Rarely, however, an intrathoracic goiter is found which has no demonstrable connection with the neck, either by glandular tissue through its vascular supply or by a fascial band. It is this tumor for which the term "complete intrathoracic goiter" should be reserved.

Fig. 3.—Photomicrograph showing numerous circumscribed areas composed of small and large acini distended with colloid.

Summary

A case of complete intrathoracic goiter without visible connection with the neck has been presented. Although similar cases have been reported, the condition is a rarity. In the reports reviewed, only seven cases were found in which no connection with the neck was described. The present case is of especial interest because of the difficulty in differential diagnosis despite radioactive iodine studies and angiocardiography. In retrospect, the angiocardiographic result can be explained on the basis of the vascularity of the tumor, which took up contrast material in high concentration directly from the aorta and resulted in the impression of "a small saccular aneurysm." Despite these studies, operation was necessary to make the diagnosis and remove the tumor.

Radioactive iodine studies were done by Dr. J. B. Workman, division of radioactive isotopes.

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DISSEMINATED COCCIDIOIDOMYCOSIS APPARENTLY CURED WITH AMPHOTERICIN B

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and
Norman F. Conant, Ph.D., Durham, N. C.

The treatment of disseminated coccidioidomycosis has previously been unsatisfactory. Although a variety of therapeutic agents have been recommended from time to time, none have had any permanent beneficial effect as the disease has pursued its relentless course. Antifungal antibiotics have been employed in recent years.[1] Nystatin has been reported to be of some benefit and has resulted in apparent cure or arrest in a few cases of the disseminated disease.[2] Recently two new antifungal antibiotics, the amphotericins A and B, have been described. They were first isolated from soil samples from the Orinoco River region of Venezuela by the action of a streptomycete.[3] Both forms have antifungal activity when administered parenterally or orally.[4] The B form appears to be more active than the A form against Coccidioides immitis and some of the other yeast-like fungi. Recent studies seem to indicate that a combination of A and B forms increases the absorption and effect of the amphotericin B.[5]

The purpose of this report is to present our experience with the use of amphotericin B in a patient with disseminated musculoskeletal coccidioidomycosis of 10 years' duration.

Report of a Case

The illness of this 34-year-old woman presumably began in January, 1946, while she was visiting in Phoenix, Ariz. She was exposed to dust while sightseeing in the nearby desert and a week or two later developed a vague respiratory infection resembling influenza. She recalls having had some chest pain, but no x-rays were made and the illness subsided spontaneously in about a week. In June, 1946, pain in the left lumbar area developed, and in August she was operated upon for what was considered to be an acute osteomyelitis, and a section of the pelvic bone was removed. Cultures were negative, and the pathological report was "granulation tissue, but no organisms seen." A small shadow in the left apex of the lung was observed about this time. The patient remained febrile, the incision failed to heal completely, and three draining sinuses persisted, in spite of extensive therapy with penicillin and sulfonamides for several months. In April, 1947, a mass formed below the incision, and in May a second operation was performed and the entire incision left open on the presumptive diagnosis of tuberculosis. Again cultures were negative. During the next year she was treated with streptomycin and penicillin but remained febrile, with temperatures of 101 to 103 F (38 to 39 C). The incision again healed only partially, leaving several draining sinuses, and new abscesses formed in the left inguinal region and around the incision. Repeated examinations for tuberculosis failed to show organisms.

In May, 1948, the patient was taken to a clinic in Cleveland, where studies for fungi were made. A diagnosis of blastomycosis was made after a positive skin test and positive complement-fixation antibodies for Blastomyces were obtained. It is not known whether she was studied for coccidioidomycosis at this time. During the next year she improved somewhat on therapy with iodides and a vaccine of blastomycin. She became ambulatory, gained weight, and her fever became low-grade, with temperatures from 99 to 101 F (37 to 38 C). Other abscesses, however, continued to form, although the infection was less acute over the next few years.

In March, 1950, the patient entered Duke Hospital for studies by the department of mycology. At this time she had a low-grade fever, and examination was normal except for the local lesions over the left hip and thigh (fig. 1). The lesion in the left lung had disappeared except for a small scar. A pure culture of C. immitis was isolated from pus aspirated from a fluctuant, nondraining area. Complement-fixation tests were slightly positive for Blastomyces and strongly positive for C. immitis. It was the opinion at this time that the patient had had coccidioidomycosis from the

From the Department of Medicine, University of Alabama Medical Center (Dr. Klapper), and the Department of Bacteriology, School of Medicine, Duke University (Drs. Smith and Conant).

start and that the positive blastomycotic studies represented a cross-reaction. Repeated examinations of the pus for tubercle bacilli were again negative.

Over the next five years, the disease was slowly progressive (fig. 2), and it was during this time that the patient moved to Birmingham, Ala. (1953) and came under the

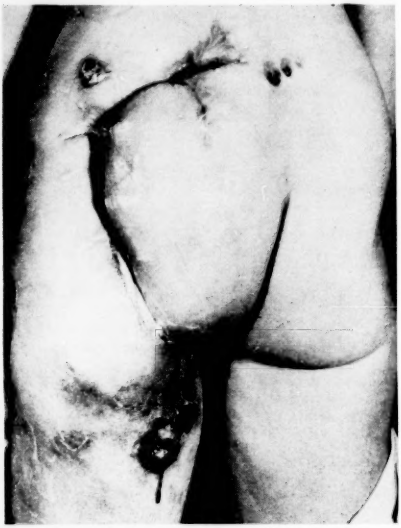

Fig. 1.—Partially healed operative site and abscesses in adjacent areas and over sacrum and posterior region of left thigh (1950).

care of one of us (M. S. K.). In this five-year period, she received various types of therapy as they were recommended for the disease. Therapy with prodigiosin had no effect and caused severe febrile reactions and thrombophlebitis at the sites of injection. In October, 1953, and January, 1955, she received one-month courses of 2-hydroxystilbamidine with no effect upon the lesions but some slight improvement in general strength. A mild trigeminal neuropathy developed after the first course, and localized thromboses occurred at the injection sites. C. immitis organisms continued to be demonstrable in the pus. The complement-fixation test remained positive at dilutions of 1:64, and the precipitin test at 1:10 for C. immitis.

During the summer of 1955 the disease became more active, fever was higher, and the patient lost weight and strength and tended to be more anemic. A large abscess formed on the right thigh, the first evidence of extension of the disease to this extremity. During the next six months the patient deteriorated physically as her disease ran a more acute course than it had for the previous five years. Four to five new abscesses formed over the right thigh and buttock, her temperature reached 102-103 F almost daily. Coccidioidin vaccine was given without effect. By January, 1956, the patient's weight was 86 lb. (39 kg.), she was able to get around only with the help of crutches or a wheel chair, and she was in constant pain. Frequent transfusions were necessary.

From January, 1956, until June, the patient was given nystatin in doses of 10 Gm. per day. On this therapy she gained 10 lb., the temperature approached its previous low-grade level, 99-101 F, and she again became ambulatory. The new lesions gradually became less painful, but there was no evidence of healing, and new abscesses continued to form. At this time the possibility of using amphotericin B was presented.

Treatment and Course with Amphotericin B.—Therapy with amphotericin B was begun in June, 1956. One gram was given orally four times daily. At this time there were 30 draining sinuses over the left buttock and thigh besides those in the incompletely healed operative site. There were eight draining sinuses over the right buttock and thigh, and one newly formed fluctuant area not yet draining. Within two weeks after institution of amphotericin B therapy, there was definite improvement in appetite and strength. The lesions were draining less profusely and the patient was afebrile. In five weeks it was apparent that the effects of the drug were dramatic. The drainage from the abscesses had changed from thick purulent material to a scant yellow watery discharge. Some of the oldest lesions were healed, the patient felt fine and was continuing to gain weight and strength. In seven weeks her weight was 114 lb. (51.7 kg.), the incision had healed over for the first time in 10 years, and all the lesions on the left side were healed over. The lesions on the right side were more persistent but were tending to heal.

Fig. 2.—Extension of disease process to left inguinal region and anterior thigh (1953).

By October, 1956, three months after beginning therapy with amphotericin B, all lesions were healed and the fluctuant area had resolved. Her weight was 120 lb. (54.4 kg.), and menses, which had ceased spontaneously two years previously, resumed. During this first three-month period of therapy, the white blood cell count gradually returned to normal, and the red blood cell count rose to normal levels (fig. 3). Liver function tests and urinalyses remained normal.

It was decided at this time, although healing appeared complete, to continue therapy for at least one year. The patient was followed periodically for the next year, and therapy was continued with amphotericin B, 1 Gm. orally four times daily, until April, 1957, at which time the drug as supplied

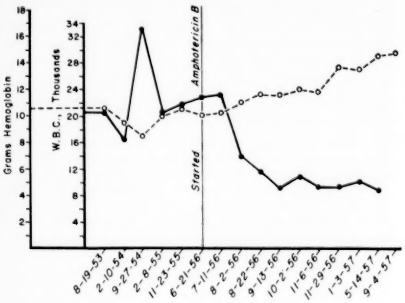

Fig. 3.—Response of white blood cell count and hemoglobin during therapy with amphotericin B.

Fig. 4.—Left oblique view of healed operative site and well-healed areas of previous abscesses of left buttock and thigh (1957).

contained amphotericin A and B with the recommendation that the dose be 2 Gm. daily. Treatment was continued through August, 1957, for a total of 14 months. As of October, 1957, the patient appeared to be in good health and the lesions remained healed (fig. 4 and 5). It is the opinion of the radiologist that the bone lesions represent an old inactive osteomyelitis involving the left ilium, sacrum, left ischium, and left femur. A slight limp and lumbar deformity are all that persist. Kidney and liver function tests are normal. The blood picture is normal. The complement-fixation for coccidioidomycosis in February, 1958, was positive at 1:16 dilution.

Comment

The correct diagnosis in this case was made serologically and by positive cultures of C. immitis. However, it was not made until four years after the onset of the disease and not until the patient had failed to respond to the therapies of the more common bacterial osteomyelitides. The significance of the mild respiratory illness during a short visit to an area endemic for coccidioidomycosis was not appreciated for many months after the onset of the disease. This important detail was recalled by the

Fig. 5.—Right oblique view of healed areas of right buttock and thigh and medial surface of left buttock and thigh (1957).

patient only upon close questioning when a diagnosis of fungus infection was entertained. The disease followed a gradually progressive course for 10 years, involving the bones and muscles, responding little or not at all to the various therapies tried. The response to amphotericin B was so definite and occurred so quickly after the institution of therapy that it seems a reasonable assumption that the healing was directly related to the therapy.

Although healing appeared to be complete in three months, long-term therapy was decided upon because of the tendency of recurrence in osteomyelitic processes and the extensive musculoskeletal involvement present. The drug was administered

orally over the entire 14-month period and was well tolerated, with no subjective side-effects. There was no evidence of untoward hepatic, renal, or hematopoietic reactions.

Summary

Apparent cure was effected, after treatment with amphotericin B, of a patient with widespread musculoskeletal coccidioidomycosis of 10 years' duration. The drug was well tolerated with no untoward effects over a 14-month period. The lesions healed within three months and were well healed one year later.

The amphotericin B and nystatin used in this study were supplied by the Squibb Institute for Medical Research, New Brunswick, N. J.

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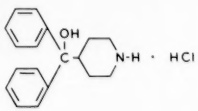
COUNCIL ON DRUGS

NEW AND NONOFFICIAL DRUGS

Monographs and supplemental statements on drugs described here and in subsequent editions of New and Nonofficial Drugs are based on the evaluation of available scientific data and reports of investigations.

H. D. KAUTZ, M.D., *Secretary.*

Azacyclonol Hydrochloride.—α,α-Diphenyl-4-piperidinemethanol hydrochloride.—α-(4-Piperidyl)benzhydrol hydrochloride.—The structural formula of azacyclonol hydrochloride may be represented as follows:



Actions and Uses.—Azacyclonol hydrochloride, a diphenylmethane, is a structural isomer of pipradrol hydrochloride, differing only with respect to the point of attachment of the piperidine ring to the methanol carbon atom. This subtle change in chemical configuration is responsible for modifying its pharmacological action; pipradrol produces overt supramedullary stimulation, whereas azacyclonol appears to reduce certain types of cerebral stimuli. The drug cannot qualify as a typical central nervous system depressant in man, however, since it does not produce any appreciable sedative or hypnotic effects even in large doses. Meager evidence for a mild depressant effect in animals is noted by the ability of azacyclonol partially to antagonize the stimulant effects of its isomer pipradrol and to prolong the sleeping time, produced by use of hexobarbital, in mice. Neither action has been confirmed in man.

The principal experimental basis in man for the present claims that azacyclonol hydrochloride is an antihallucinatory agent stems from experiments reported to demonstrate an antagonistic effect against the confusion and auditory and visual hallucinations induced in human volunteers by mescaline and lysergic acid diethylamide (LSD 25). Subsequent studies attempting to confirm these observations have been unsuccessful.

The clinical trials stemming from these experiments were initiated because of a postulated relationship between drug-induced hallucinations and those associated with natural disorders, a hypothesis which remains to be proved. Results of clinical trials with azacyclonol in patients with hallucinations and confusion have been highly variable. Some investigators report decidedly beneficial results in some, but not all, patients; other workers find the drug entirely without value. On the basis of the more favorable reports, it would appear that azacyclonol is most likely to be useful in acute schizophrenia and toxic states; it has been of less

value in chronic schizophrenia and has no place in the treatment of psychotic depressive states, obsessive-compulsive disorders, or anxiety reactions. In general, most of the earlier favorable reports are based on studies over relatively brief periods of observation and are largely uncontrolled. More recent observations in chronic schizophrenia suggest that with longer duration of therapy (four to six weeks), in which oral doses of 100 mg. per day are used, a larger number of favorable responses may be obtained than with placebo controls in reducing the incidence of hallucinations, delusions, assaultiveness, agitation, and seclusiveness.

On the basis of both laboratory studies and clinical experience, the toxicity of azacyclonol hydrochloride seems to be negligible. Even in very large doses, both intravenous and oral, the drug has not produced any serious untoward reactions or side-effects. Rarely, a maculopapular skin rash has been observed which is reversible upon discontinuation of therapy.

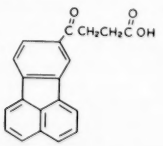
Dosage.—Azacyclonol hydrochloride is administered orally or intravenously. There is no unanimity regarding the effective dosage. Hence, proposed oral dosage for the treatment of acute schizophrenic hallucinosis varies from as little as 20 mg. to as much as 100 mg. three times daily. For schizophrenic patients in whom oral medication is not feasible, 100 mg. of the drug is suggested by direct intravenous injection or slow intravenous drip. For the treatment of toxic psychoses, such as postoperative confusion or delirium tremens, the proposed intravenous dose is 100 mg. every eight hours for one to seven days. Until more evidence can be accumulated to support the therapeutic value of the drug, the foregoing proposed dosages should be considered experimental.

Preparations: tablets 20 mg. and 100 mg.; solution (injection) 20 mg. in 1 cc.

Applicable commercial name: Frenquel.

The Wm. S. Merrell Company cooperated by furnishing scientific data to aid in the evaluation of azacyclonol hydrochloride.

Florantyrone.—γ-Oxo-γ-(8-fluoranthene) butyric acid.—The structural formula of florantyrone may be represented as follows:



Actions and Uses.—Florantyrone is a synthetic substance which, although chemically unrelated to the natural bile salts, produces the pharmacological effects of dehydrocholic acid and related compounds. The drug causes an increase in the volume of bile without stimulating evacuation of the gallbladder or increasing the quantity of total bile solids. Hence, florantyrone is properly classified as a hydrocholeretic agent. The bile produced by administration of this agent is usually deep green in color, low in sediment, and of low viscosity.

Florantyrone has been proposed for use in the medical management of chronic cholecystitis and cholangitis and in the prevention of cholelithiasis. From a theoretical point of view, the production of a copious flow of thin bile may be of value to encourage drainage of the bile ducts by removal of mucus and inspissated bile and debris and to discourage the ascent of infection. However, available clinical studies do not demonstrate the effectiveness of florantyrone in cases in which the gallbladder does not fill and in the presence of stasis of the biliary ducts.

Florantyrone and other hydrocholeretics also have been employed for the treatment of so-called biliary dyskinesia. This condition is supposedly characterized, in part, by hypertonicity of the biliary musculature, resulting in spastic obstruction to the flow of bile. Since it is questionable whether such a clinical entity does, in fact, exist, it is difficult to interpret the significance of case reports of patients with biliary dyskinesia who are alleged to have responded favorably to florantyrone. In the absence of controlled observations, the benefits claimed in biliary dyskinesia may well have been psychological. Nevertheless, some clinicians advocate a trial of the drug in conjunction with antispasmodic agents in cases in which spasm of the sphincter of Oddi is suspected.

Florantyrone is reported to be useful for the treatment of postcholecystectomy syndrome. Although this is a difficult diagnosis to make or refute, the majority of patients treated for this condition showed some degree of symptomatic improvement. Since slow improvement is to be expected after such an operation without treatment by florantyrone, there is no convincing evidence that the improvement cited was due to the drug. However, there may be some validity to the concept that postoperative therapy to increase the flow of bile may compensate to some extent for the missing bile reservoir removed at surgery. There is no doubt that a copious flow of thin bile is helpful in removing small stones or other foreign material overlooked at operation. In patients with T-tube drainage after choledochoplasty, the drug is of considerable value in maintaining the patency of the tube, by preventing or diminishing the amount of incrustation and inspissated material which may form.

There is no valid evidence that florantyrone is useful in the treatment of hepatic dysfunction. The wisdom of employing this or any other hydrocholeretic in the presence of severe hepatitis is questionable. The toxicity of florantyrone is low and its margin of safety wide. As with other hydro-

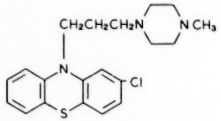
choleretics, the drug may produce some diarrhea. It may also aggravate pruritus in patients with some forms of partial intrahepatic or extrahepatic biliary obstruction.

There is no report of liver toxicity in patients with normal hepatic function. Since the drug is likely to be used in patients with chronic hepatic or biliary tract disease and for long periods of time, further investigation for possible harmful effects in such patients and under such conditions is indicated. Because it increases the flow of bile, florantyrone is contraindicated in patients with complete mechanical biliary obstruction. It should not be used in the presence of acute cholecystitis.

Dosage.—Florantyrone is administered orally. The usual dose for adults ranges from 750 mg. to 1 Gm. daily.

Preparations: tablets 250 mg.
Applicable commercial name: Zanchol.
G. D. Searle & Co. cooperated by furnishing scientific data to aid in the evaluation of florantyrone.

Prochlorperazine.—2-Chloro-10-[3-(1-methyl-4-piperazinyl)propyl]phenothiazine.—The structural formula of prochlorperazine may be represented as follows:

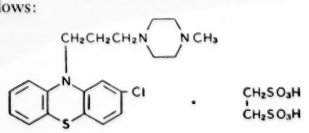


Actions and Uses.—Prochlorperazine has the same actions and uses as prochlorperazine maleate except that it is administered rectally. (See the monograph on prochlorperazine maleate.)

Dosage.—For rectal administration, the suggested dose for adults is one 25-mg. suppository twice daily. Rectal dosages for children are as follows: up to 2 years of age, one-half to one 5-mg. suppository twice daily; ages 2 to 6, one 5-mg. suppository twice daily; ages 6 to 12, one to two 5-mg. suppositories twice daily.

Preparations: suppositories 5 mg. and 25 mg.
Applicable commercial name: Compazine.
Smith, Kline & French Laboratories cooperated by furnishing scientific data to aid in the evaluation of prochlorperazine.

Prochlorperazine Ethanedisulfonate.—2-Chloro-10-[3-(1-methyl-4-piperazinyl)propyl]phenothiazine ethanedisulfonate.—The structural formula of prochlorperazine ethanedisulfonate may be represented as follows:

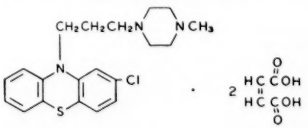


Actions and Uses.—Prochlorperazine ethanedisulfonate has the same actions and uses as prochlorperazine maleate except that it may be administered intramuscularly as well as orally. Parenteral therapy is usually reserved for the treatment of severe nausea and vomiting, for the immediate control of acutely disturbed psychotics, or for patients who cannot be relied upon to take oral medication. (See the monograph on prochlorperazine maleate.)

Dosage.—Prochlorperazine ethanedisulfonate is administered orally or by deep intragluteal injection. Oral dosage for adults and children is the same as that outlined in the monograph on prochlorperazine maleate. For severe nausea and vomiting, the usual intramuscular dose for adults is 5 to 10 mg. every three to four hours. No more than 40 mg. should be injected in any 24-hour period unless the patient is hospitalized and under adequate observation. For control of acutely disturbed patients, the suggested intramuscular dose is 10 to 20 mg. repeated at intervals ranging from one to six hours, depending on individual clinical response. For all indications, the usual intramuscular dose for children is 0.10 mg. per pound of body weight. Oral therapy should be substituted as soon as feasible.

Preparations: solution (injection) 10 mg. in 2 cc., 50 mg. in 10 cc.; syrup 1 mg. per cc.
Applicable commercial name: Compazine Ethanedisulfonate.
Smith, Kline & French Laboratories cooperated by furnishing scientific data to aid in the evaluation of prochlorperazine ethanedisulfonate.

Prochlorperazine Maleate.—2-Chloro-10-[3-(1-methyl-4-piperazinyl)propyl]phenothiazine dimaleate.—The structural formula of prochlorperazine maleate may be represented as follows:



Actions and Uses.—Prochlorperazine maleate is a phenothiazine compound with actions and uses similar to those of chlorpromazine to which it is related chemically. On a weight basis, prochlorperazine is considerably more potent than chlorpromazine, and comparable therapeutic effects may be achieved with doses which are approximately one-fifth those of the latter agent. The drug produces less adrenergic blockade and consequently less hypotension than does chlorpromazine. It also exerts mild antihistaminic and antispasmodic effects. Unlike chlorpromazine, its potentiating action on other central nervous system depressants is minimal and may be clinically insignificant. The precise mechanism of action, metabolic fate, and excretion of prochlorperazine are not known.

Prochlorperazine maleate is employed for the treatment of those neuroses and mild emotional disturbances in which anxiety, tension, and agitation predominate. The drug is apparently capable of alleviating this type of mental stress and of lessening motor activity in a sizable percentage of patients. Prochlorperazine maleate has also been employed in severe psychiatric disorders such as schizophrenia, mania, involutional psychoses, degenerative conditions, and senile and toxic psychoses. On the basis of subjective observations, the drug appears to be useful in many such cases. Beneficial results ascribed to its action include, among others, reduction in psychomotor agitation and excitement, diminished aggressiveness and destructiveness, loss of hallucinations and delusions, and a general calming effect. The drug has also been used successfully in some cases of psychomotor retardation marked by apathy and lethargy. Prochlorperazine maleate is effectively employed as an antiemetic, and for this purpose it exhibits a potency of about four to five times that of chlorpromazine. Accordingly, it may be used for the control of mild or severe nausea and vomiting due to a variety of causes.

In general, the over-all clinical toxicity of prochlorperazine appears to be somewhat less than that of chlorpromazine. In the usual therapeutic dosage range, side-effects are generally infrequent, mild, and transitory. These include sedation, dizziness, hypotension, tachycardia, and xerostomia. Rarely, a skin reaction, tinnitus, vertigo, nasal congestion, miosis, or gastric hyperacidity may occur. Prochlorperazine also compares favorably with chlorpromazine with respect to the infrequent occurrence of orthostatic hypotension, sedation, and lethargy. To date, no jaundice or blood dyscrasias have been reported; however, in view of the phenothiazine structure of the drug, physicians should be alert to this possibility. On the other hand, neurological sequelae referable to extrapyramidal involvement may be troublesome at higher dosages and not infrequently complicate therapy with prochlorperazine. Symptoms are Parkinsonian-like in character and include spasticity and painful constriction of skeletal muscles, chiefly those of the head, neck, and shoulders. Such effects are most frequent when high doses are used but have occurred with even moderate dosage. Hence, adequate observation of the patient is necessary. If extrapyramidal symptoms appear, they may be controlled by either a downward adjustment of dosage, by the concomitant administration of an antiparkinson drug, or by temporary withdrawal of prochlorperazine.

Dosage.—Prochlorperazine maleate is administered orally. In mild and moderate emotional disturbances and in nausea and vomiting, the oral dose for adults ranges from 5 to 10 mg. three or four times daily. In more resistant cases, the dosage may be increased gradually until symptoms are controlled or side-effects become bothersome. The suggested initial oral dose for the treatment of institutionalized psychotic patients is 30 to 40 mg. per day in divided doses. This is then increased gradually until the desired response has been obtained. The usual effective dose for such patients is 75 to 125 mg. daily.

For infants and children up to 2 years of age, the usual oral dose is 0.25 mg. per pound of body weight one or two times daily but not exceeding a total of 15 mg. per day. Doses of 5 mg. two or three times daily but not exceeding 20 mg. per day may be given to children between the ages of 2 and 6. For children between 6 and 12 years of age, the usual oral dose is 5 mg. two or three times daily, but it should not exceed a total of 25 mg. per day.

Preparations: capsules (sustained-release) 10, 15, and 30 mg.; tablets 5, 10, and 25 mg.

Applicable commercial name: Compazine Dimaleate.

Smith, Kline & French Laboratories cooperated by furnishing scientific data to aid in the evaluation of prochlorperazine maleate.

CAUSAL FACTORS IN HYDRONEPHROSIS.—The author endeavored to determine the causal factors in 104 hydronephrotic kidneys, and he concluded that accessory vessels which constrict the pelvi-ureteric junction or the upper end of the ureter were responsible in half of these cases. In the other half, something that upset the normal muscular action of the renal pelvis or the upper ureter was responsible. In many cases the pelvic musculature appeared to be incapable of normal rhythmic contraction; it contracted in segments and appeared to fibrillate. In many cases the ureter adjacent to the pelvi-ureteric junction appeared to be in persistent spasm, and rhythmic contraction was arrested at this point. Congenital anomalies such as malrotation, horse-shoe kidney or retrocaval ureter accounted for a few cases, but organic stenosis or stricture was seldom responsible. The condition appeared to be bilateral in 50 per cent of cases, although in most instances it was more evident on one side.—J. C. Anderson, O.B.E., T.D., F.R.C.S., The Treatment of Hydronephrosis, *The British Journal of Clinical Practice,* January, 1958.

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OPTIMAL BIRTH WEIGHTS

THE U. S. Department of Health, Education, and Welfare, through the National Office of Vital Statistics of the Public Health Service, has issued a study of births and neonatal deaths by birth weight.[1] The data cover the period 1952-1954, and all but one of the states are represented. This study was made possible by adding an item on birth weight to the birth certificates formerly in use. The addition was made by most states in 1949, and by 1950 nearly all had included it. It thus became possible to obtain extremely valuable information on the relation of mortality to birth weight by matching birth and death records.

One difficulty encountered in this study deserves comment because it so often besets the statistician who tries to work with data supplied by collaborators from other fields. This difficulty, the problem of false modes, is noted by the authors in connection with data on length of gestation periods. A false mode is caused by measurements that appear oftener than they should because of some fault in the way the original observations were reported. In the present study, the information on gestation showed an abnormal frequency of 40-week periods. This must be interpreted to mean that some physicians, reporting births, failed to calculate a period of gestation for newborn infants who appeared to be normally developed. There was also an abnormally high proportion of gestation periods reported as 36 weeks, presumably due to an erroneous conversion from months to weeks by multiplying by 4. It is evident that accurate data on gestation periods will not be available until physicians everywhere, in reporting individual births, are able to supply the actual, instead of the estimated, time in every case.

An important result of the tabulation of mortality against birth weight is the finding that in most states the lowest neonatal mortality occurs in the group of babies weighing between 3,501 and 4,000 Gm. In four states the minimal mortality was in the next heavier group, between 4,001 and 4,500 Gm. Further detailed study would be required to locate the minimum exactly and to tell whether the differences among states had any significance, but it is evident that there exists an optimal birth weight and that it lies nearer to 4,000 than to 3,501 Gm. To locate it more exactly would require more elaborate methods. Moreover, the neonatal mortality (that is, the rate of deaths under 28 days per 1,000 live births) is only one of the possible criteria by which the optimal birth weight could be judged. The point is, however, that the present tabulations suffice to show that an optimal birth weight exists.

The tabulations show that, during the period 1952-1954, the births in the 3,001 to 3,500 Gm. category numbered 4,308,726. This is the largest group, since the corresponding figures for the 3,501 to 4,000 and 2,501 to 3,000 Gm. groups were 3,036,137 and 2,076,134 respectively. It would appear that the modal and optimal groups do not coincide. It is inevitable that many babies will be born before they attain the optimal birth weight, but at first glance these figures seem to indicate that too many babies fail to attain it. There have been ample warnings, of late, concerning the dangers of elective induced labor and the handicaps of the "unfinished child." The problem of defining and locating the optimal birth weight is therefore of great importance. Physicians everywhere can help to solve it by supplying the most accurate data possible when filling out birth certificates.

The data illustrate the fact that prematurity is more frequent, and more important as a cause of fetal wastage, than is postmaturity. Because figures for postmaturity are less abundant, the effects of postmaturity on neonatal mortality have been more difficult to follow statistically. Nevertheless they are important, and the dilemmas that confront the physician when he has to deal with a case of prolonged gestation have been discussed recently by Nesbitt,[2] Kohl,[3] Clifford,[4] and others. A more detailed analysis of the national data on neonatal mortality as related to longer gestation periods and for birth weights exceeding 4,501 Gm. seems desirable. It should afford a valuable guide for physicians in judging the risk involved when babies are overdue.

1. Births and Neonatal Deaths by Birth Weight: Reporting Areas, 1952-54, Vital Statistics **47**:1-19 (Dec. 16) 1957.
2. Nesbitt, R. E. L., Jr.: Postmature Pregnancy—Clinical Obstetric Aspects, J. A. M. A. **165**:1656-1658 (Nov. 30) 1957.
3. Kohl, S. G.: Oxygen Levels in Postmature Fetus, J. A. M. A. **165**:1659-1662 (Nov. 30) 1957.
4. Clifford, S. H.: Pediatric Aspects of Placental Dysfunction Syndrome in Postmaturity, J. A. M. A. **165**:1663-1665 (Nov. 30) 1957.

ORGANIZATION SECTION

SAFEGUARDING M.D. CREDENTIALS

Come H-bomb or high water, physicians everywhere will be able to prove their qualifications, under a medical credentials program to be launched at the A. M. A. Annual Meeting next month. The first applications for placing medical credentials in well-protected repositories will be accepted at the World Medical Association's booth in the A. M. A. Scientific Exhibit at San Francisco, from June 23 to 27. At least two repository sites in different parts of the world are contemplated in case one is wiped out in war or other catastrophe.

Doctors will fill out the detailed application blanks in triplicate, attaching passport-type photographs and their thumb prints. These, along with copies of medical school and licensure credentials, will be sent to the WMA secretariat in New York City. There, each set of data will be assigned a file number for the registered physician, and will be stored in a repository. Credentials could be withdrawn through presentation of the file number with proper identification. The cost for physicians between the ages of 25 and 34 is $60 for life. There is a 10-year service rate for older doctors.

Details of the central repository program were announced early this month by Dr. Walter C. Bornemeier, chairman of the WMA's United States Committee for Northern Illinois, at the annual convention of the Student American Medical Association. It was the S. A. M. A. which first suggested a central repository system for credentials. Dr. Bornemeier told the student House of Delegates in Chicago on May 1:

"Unless the doctors of the world avail themselves of this service, your resolution and the four years spent in implementing it become meaningless. I would like to suggest that you consider appointing a permanent committee to develop and promote a satisfactory educational program for informing every future doctor of the untold value he may realize by depositing copies of his professional credentials in the central repository.

"As you know, during World War II and the recent Hungarian tragedy hundreds of doctors left their countries. Their medical credentials were lost or destroyed. Today many of them are laborers, research assistants or hospital service personnel because they have no means of proving that they are medically trained and fully accredited to practice medicine. Even in a holocaust less frightful than war your credentials might be lost or stolen and you would find it difficult or greatly inconvenient to replace them."

Dr. Louis H. Bauer, secretary general of the WMA, which is a confederation of 53 national medical associations representing more than 700,000 physicians throughout the world, has said: "Success in this one program alone—a central repository for medical credentials—would justify the existence of WMA."

Other WMA objectives include promotion of a freer medical practice; support of freely functioning medical practice; establishment of national medical organizations where none exist; promotion of medical research; universal adoption of a special emblem that will identify and protect civilian medical units in time of armed conflict; the monitoring of activities of more than 23 other international organizations as they affect the practice of medicine; formulation of principles of cooperation among practicing physicians and public health officers; and sponsorship of world conferences on medical education.

NEW A. M. A. PUBLICATIONS

Pamphlets on "Health Aspects of Aging" and on "Suggested Guides to Relationships Between Medical Societies and Voluntary Health Agencies" now are available for distribution to physicians and other interested individuals. Mailing began late in April.

The booklet on aging, prepared by the A. M. A. Committee on Aging under the Chairmanship of Henry B. Mulholland of Charlottesville, Va., is a compilation of articles which appeared as a series in THE JOURNAL during the past year. Each author is a recognized authority on the subject selected, and has endeavored to minimize technical terminology in order to gain acceptance by a large number of readers.

The A. M. A. Committee on Relationships Between Medicine and Allied Health Agencies, whose Chairman is Sidney J. Shipman of San Francisco, prepared the other pamphlet as a revision of a draft which also had appeared in THE JOURNAL. An introduction of these "Suggested Guides" takes note of the widespread growth of voluntary health agencies, and it adds:

"Physicians, because of their special training, recognize they have a singular responsibility as guardians of the individual's and nation's health. Physicians also recognize a national emotional re-

sponse by individuals toward pleas for help to aid the unfortunate. There comes a time, however, when those activities which arouse natural emotional responses should have some evaluation and guidance."

Copies of either or both of the two pamphlets may be obtained from the Council on Medical Service, American Medical Association, 535 N. Dearborn St., Chicago 10.

DR. ROBERT E. WILSON HONORED FOR AID TO MEDICAL EDUCATION

Medical Education Week was highlighted in the Chicago area April 21, at a luncheon in the Drake Hotel honoring Robert E. Wilson, Sc.D., LL.D., retired chairman of the Standard Oil Company (Indiana), for his leadership in developing aid-to-medical-education programs among corporations. The luncheon, sponsored by the Association of American Medical Colleges, the National Fund for Medical Education, and the American Medical Association, was attended by 250 corporation executives, physicians, and medical educators.

Pictured are, *left to right*, Drs. George F. Lull, President, American Medical Education Foundation, Robert E. Wilson, Stanhope Bayne-Jones, and F. J. L. Blasingame, General Manager of the American Medical Association.

Dr. Wilson, in accepting a citation of merit presented by Lowell T. Coggeshall, M.D., AAMC president, estimated that American industry's gifts to health, education, and welfare totaled more than half a billion dollars last year. He said the financial needs of higher education is a joint responsibility of industry, the government, foundations, and the public. "We should consider the difference between what we are doing and what we should be doing—or the difference between what we have in the way of health and security and what we could do," he said.

Dr. David D. Henry, president of the University of Illinois, presided at the luncheon and introduced the principal speaker, Stanhope Bayne-Jones, M.D., chairman of the Secretary's Consultants on Medical Research and Education of the U. S. Department of Health, Education, and Welfare.

Dr. Bayne-Jones warned that low faculty salaries are weakening the basic science departments of the nation's medical schools, and the situation in the medical schools is particularly serious at this time because of the added pressures on the schools resulting from the current revolution in science through the study of the atom, the cell, and nuclear physics.

"It may be predicted that this trend will continue, and at an increased rate as new schools are developed, if salaries of teachers in these departments fail to maintain a reasonable matching of salaries paid in competitive organizations," he said.

The luncheon was part of the nationwide observance of Medical Education Week, April 20-26, sponsored by medical schools and state and county medical societies.

"WIDE WIDE WORLD" COMMENDED

The Board of Trustees of the American Medical Association has commended the National Broadcasting Company and its Sunday afternoon feature, "Wide Wide World," for its program on American doctors. This program presented "The House I Enter," the story of American doctors, on Sunday, Oct. 27, 1957.

The Board commendation read: "Through the miracle of television, 'Wide Wide World' took a vast audience of televiewers around the country to see the work being done by doctors in various types of medical practice. The medical profession is grateful for this opportunity to report its activities to the American people."

A special citation was also issued to Ted Rogers, who produced the show. "Wide Wide World" is sponsored by General Motors and is seen over the full NBC television network each Sunday from 4:00 p. m. to 5:30 p. m. EST.

CHANGE OF ADDRESS

If you change your address please notify THE JOURNAL at least six weeks before the change is made. Include the address label clipped from your latest copy of THE JOURNAL, being sure to clearly state both your old and new address. If your city has Postal Zone Numbers, be sure to include this Zone Number in your new address.

MEDICAL NEWS

ILLINOIS

Hospital Lecture.—The final lecture in the eighth annual North Shore Hospital lecture series on Emotional Problems of Childhood will be held June 4, 8 p. m., on "Management of the Emotional Problems of the Physically Handicapped Child," by Dr. William Cooper, assistant professor of clinical surgery, Cornell University Medical School, New York City. The Commission on Education of the American Academy of General Practice has approved these lectures for category II credit.

Appoint Director of University Health Service.—Dr. Orville S. Walters, of Danville, has been named director of the University of Illinois Health Service. Dr. Walters, staff psychiatrist at the Hospital in Danville, will take over his new duties Aug. 1. He was president of Central College, McPherson, Kan., from 1939 to 1944, when he entered private practice. In 1953 he became associated with the Veterans Administration. Dr. Walters succeeds Dr. Lester M. Dyke, who resigned last year to become head of the health service at University of Maryland, Baltimore.

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Chicago

Dr. Newman Honored.—Dr. Louis B. Newman, chief of the physical medicine and rehabilitation service, VA Research Hospital, recently received the "Civil Servant of the Year" award from the Federal Personnel Council and Regional Council of Federal Agencies. He was selected from among 70,000 civil service employes in the Chicago area. Dr. Newman is president-elect of the American Academy of Physical Medicine and Rehabilitation and is on the executive committee, Section on Physical Medicine, American Medical Association.

Dustfall in Chicago.—The Armour Research Foundation of the Illinois Institute of Technology, in its report of the amount and chemical analysis of the dustfall for Chicago for March, has announced that the average dustfall at its 25 stations, including the Loop, was 45.6 tons per square mile per month of 30 days. Of this amount 23.4 tons were water insoluble constituents and 22.2 tons were water soluble constituents. The "Loop Average" total dustfall was 94.6 tons per square mile. The least amount of dustfall was 21.8 tons per square mile at a station in the near-north section of the city.

Gastroenteritis in a Hospital.—The U. S. Public Health Service's Morbidity and Mortality Weekly Report, released May 2, notes that Dr. Olga G. Brolnitsky, Chicago Board of Health, reported an outbreak of gastroenteritis in a hospital where 51 persons became ill with nausea, vomiting, cramps, and diarrhea, three to seven hours after eating a luncheon of tuna-fish salad. Of the 51 food handlers investigated, Salmonella was recovered from the stools of two persons, Shigella from the stool of another, and coagulase-positive Staphylococcus was cultured from the throats of four others. These seven employees were removed from their jobs and hospitalized.

Grant to Insure Salary Until Retirement.—The American Cancer Society has made a grant to the University of Chicago of $587,344, specifically allocated to pay the salary until he reaches retirement age of 34-year-old Dr. Paul Talalay, associate professor of biochemistry in the university's Ben May Cancer Research Laboratory. According to *Tower Topics*, published by the university for its alumni, the grant is part of a program designed "to lure the most brilliant young scientists in the country to fight cancer." It is said to be probably the largest grant ever awarded to a single individual by a voluntary agency. Dr. Talalay's earlier discovery and isolation of enzymes involved in the utilization of sex hormones by the body won him the Theobold Smith Award in Medical Sciences.

Dr. Huggins Receives German Honor.—Dr. Charles B. Huggins, director of the Ben May Laboratory for Cancer Research of the University of Chicago's medical and biological research center, has been named to membership in the Order of Pour le Merite by the German Federal Republic. Founded by Frederick the Great as a military honor, it now provides recognition in the sciences and arts, with membership in the group limited to 30. Thornton Wilder, author and playwright, and Arthur H. Compton, physicist, are the only two other American members. President Theodor Heuss of the German Federal Republic will install Dr. Huggins and the other newly elected member, Dr. Georg von Hevesy, professor of chemistry and physics in the Universities of Copenhagen and Stockholm, in a ceremony at Bonn July 7.

Physicians are invited to send to this department items of news of general interest, for example, those relating to society activities, new hospitals, education, and public health. Programs should be received at least three weeks before the date of meeting.

MASSACHUSETTS

Grant for Study of Birth Process.—A grant of $400,000 to the Harvard Medical School and the Boston Lying-In Hospital for basic studies in problems surrounding the origin of life and the birth process has been made by the Association for the Aid of Crippled Children. The grant is in addition to $371,000 previously voted by the association to support work in the same general area at the university. The money will be available over a 10-year period and will support a coordinated program of research and teaching devoted especially to problems associated with the beginning and early development of human life. Dr. Duncan E. Reid, professor of obstetrics, Dr. Clement A. Smith, associate professor of pediatrics, and Claude A. Villee, Ph.D., associate professor of biological chemistry, will be responsible for the program.

Dr. Malamud Named Research Director.—Dr. William Malamud will resign as chairman of the division of psychiatry at Boston University School of Medicine and as psychiatrist-in-chief at the Massachusetts Memorial Hospital, Sept. 1, to accept the post of research director for the National Association for Mental Health. Under Dr. Malamud's direction the NAMH research committee will allocate grants to research scientists investigating the cause, treatment, and prevention of mental and emotional ailments. The new program will be supported at first by a minimum allocation of 5% of the association's annual fund-raising campaign receipts. Dr. Malamud's career includes professorships at the University of Iowa, Iowa City, and Tufts Medical School, Boston. He is secretary of the American Psychiatric Association; director of research, Scottish Rite and National Association for Mental Health Committee on Schizophrenia Research; director, American Board of Psychiatry and Neurology; and consultant to the Ohio State Department of Mental Hygiene and the Boston Veterans' Hospital.

MICHIGAN

Appoint Professor of Physical Medicine.—Dr. Joseph N. Schaeffer has been appointed as special professor of physical medicine, Wayne State University, Detroit. A new department of physical medicine was created at the College of Medicine when his appointment became effective May 3. Dr. Schaeffer, of Peoria, Ill., was recently named director of the Rehabilitation Institute of Metropolitan Detroit. He served as a medical officer in the Air Force from 1942 to 1953. He is a diplomate of the American Board of Physical Medicine and Rehabilitation.

Personal.—Dr. Archer A. Claytor, of Saginaw, has received notice of his appointment to the board of directors of the Virgin Islands Corporation, announced Jan. 25 by President Eisenhower. Virgin Islands Corporation is a government corporation which promotes development of industry and trade in the islands. Among other things, it is engaged in sugar production, electric power production, promotion of tourist trade, and soil and water preservation.——Dr. Austin W. Heine, Mount Clemens, has been awarded the American Legion's Citizen of the Year award for "outstanding service to the community, state and nation."

MINNESOTA

Medical School Admissions to Increase.—Admissions to the University of Minnesota Medical School, Minneapolis, will be increased from 125 to 140 students for the next school year (1958-1959) and to 150 in 1959, Dr. Robert B. Howard, associate dean, has announced. By 1962, the four medical school classes will have a combined total enrollment of about 600, as compared with under 500 at present. Enlarged laboratory facilities and strengthening of the staffs of the university's basic medical sciences departments are the principal factors which permit the increases.

University News.—Dr. Takeo Hayashida, a member of the surgical faculty of the University of Tokyo, visited the Mayo Clinic and Mayo Foundation at Rochester Jan. 20-23, observing intracardiac surgical procedures and clinical and experimenal vascular surgery. On returning to Japan, he will become head of a new department of intracardiac and vascular surgery.——Dr. Grant H. Lathe, of the department of chemical pathology, University of Leeds School of Medicine, England, discussed recent work on the chemistry of jaundice at the Mayo Clinic and Mayo Foundation, Rochester, March 12.

MONTANA

Annual Conference at Missoula.—The annual Western Montana Medical and Surgical Conference, sponsored by the Western Montana Medical Society, will be held June 28 at the Hotel Florence, Missoula. Dr. Eugene J. P. Drouillard, president of the society, will open the meeting with an address. Two panel discussions are scheduled: "The Cytologic Diagnosis of Uterine Cancer" and "Some Blood Disorders in General Practice," moderated by Drs. Glenn A. Carmichael and Bryce D. Colwell, of Missoula, respectively. The following will be presented by guest speakers:

Ovarian Tumors, Dr. Clifford L. Fearl, Portland, Ore.
Leukemia, Dr. Claude E. Forkner, New York City.
Uterine Bleeding, Dr. Fearl.
The Philosophy for the Practice of Medicine, Dr. Forkner.

The program has been submitted for eight hours of credit by the American Academy of General Practice. A program of ladies' activities is arranged. For information write the Western Montana Clinic, Owen and West Broadway, Missoula, Mont.

NEW YORK

Dr. Vaughan to Head Immunology Program.—Dr. John H. Vaughan, on the medical faculty of the Medical College of Virginia, Richmond, will join the University of Rochester School of Medicine and Dentistry July 1 to head a new training and research program in clinical immunology. Dr. Vaughan has been appointed associate professor of medicine and assistant professor of bacteriology and immunology in the Medical School, and senior associate physician in Strong Memorial Hospital. Four of Dr. Vaughan's research associates will move from Richmond to Rochester with him: Dr. and Mrs. Richard W. Dutton, of London, England; Dr. Mariam George, of Bombay, India; and Dr. Jean L. Harris.

Three Named Professors at Rochester.—Three members of the University of Rochester Medical School faculty who have been on the department of medicine faculty for 30 years or more have been promoted to full professors: Dr. Lawrence A. Kohn, first chief resident in medicine at the Medical Center when it was opened Jan. 21, 1926, named clinical professor of medicine, the first to be given that title; Dr. Ernest H. Keutmann, who came to the Medical Center as an intern in Strong Memorial Hospital in 1928; and Dr. Paul H. Garvey, who has been in charge of the neurology section since 1928. Dr. Kohn (in 1956) and Dr. Garvey (in 1957) have been awarded the Gold Medal of the Medical School Alumni Association for "inspiring teaching, integrity, and devotion to students." Dr. Kohn came to Strong Memorial Hospital in 1925 as an instructor in medicine. He became an assistant professor (1929) and associate professor in the Medical School and associate physician in Strong Memorial Hospital (1941). In 1956 he received the Award of Merit of the Rochester Academy of Medicine. Dr. Garvey came to the Medical School as an instructor in medicine from the University of Michigan, Ann Arbor, where he had been an instructor in neurology. He was promoted to assistant professor and assistant physician in 1930, and to associate professor and associate physician in 1937. Dr. Keutmann was appointed an assistant in medicine and assistant resident physician in 1929 and rose to instructor and resident physician in charge of the medical outpatient department in 1930, assistant professor of medicine and pharmacology in 1947, and associate professor in 1948.

New York City

Personal.—Dr. Howard A. Rusk of the department of physical medicine and rehabilitation, New York University–Bellevue Medical Center, was recipient of a bronze plaque "for his services to the mentally retarded" at the annual dinner of the Association for the Help of Retarded Children May 18.—Dr. William E. Studdiford, professor emeritus of obstetrics and gynecology, New York University College of Medicine, received the New York University presidential citation at a reception in his honor April 11. The presentation was made "in recognition of Dr. Studdiford's outstanding services to the University and for his high professional attainment within his specialty prior to his retirement in September, 1956, as professor and chairman of the department of obstetrics and gynecology."—Dr. Frank G. Boudreau, who received the Albert Lasker Award in 1957 for "outstanding contributions in public health administration," has been elected president of the National Vitamin Foundation.

OHIO

State Medical Election.—The Ohio State Medical Association has installed the following officers: Dr. George A. Woodhouse, Pleasant Hill, president; Dr. Frank H. Mayfield, Cincinnati, president-elect; and Dr. George J. Hamwi, Columbus, reelected treasurer for a three-year term. The following were elected to the Council for the first time: Dr. Charles W. Hoyt, Cincinnati, first district, and Dr. Floyd M. Elliott, Ada, third district. The 1959 meeting will be held in Columbus the week of April 19.

Plan Memorial for Dr. Paryzek.—Staff members at St. Alexis Hospital, Cleveland, and friends are planning a memorial to Dr. Harry V. Paryzek, who was president of the Ohio State Medical Association in 1941-1942. The memorial is to be a $125,000 penthouse conference room atop the five-story service wing which is to be built with the proceeds of the St. Alexis Hospital Million Dollar Building Improvement Fund Campaign. Dr. Harold J. Barker is chairman of the memorial committee. Dr. Paryzek, who served in Europe during World War I, became director of medicine at St. Alexis Hospital and chief of staff in 1930. In 1933 he was president of the Cleveland Academy of Medicine, and at the time of his death was chairman of the state medical association's Committee on Chronic Illness. For information write The Harry V. Paryzek Memorial Fund, c/o St. Alexis Hospital, 5163 Broadway, Cleveland 27.

OREGON

Bacteria in Cream-Filled Doughnuts.—The U. S. Public Health Service's Morbidity and Mortality Weekly Report, released May 2, notes that Dr. Samuel B. Osgood of the Oregon State Board of Health, reported an outbreak of gastroenteritis in four persons in a family after eating cream-filled doughnuts from a bakery. A 5-day-old doughnut obtained from the home had a bacterial count of 850,000,000 per gram, while a fresh doughnut from

the bakery had a bacterial count of 6,200,000 per gram. The bakery discontinued making cream-filled products, and all of their equipment was disinfected.

PENNSYLVANIA

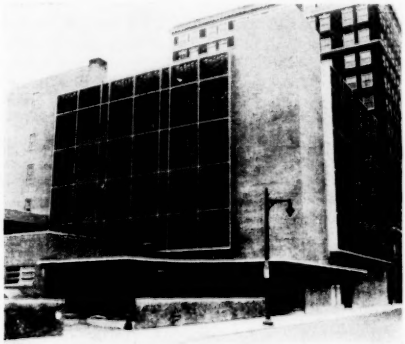
Hospital News.—A suite of climate-simulating rooms being constructed for Lankenau Hospital, Overbrook, will enable scientists to study body metabolism. The suite will consist of three rooms with minutely controlled temperatures and humidities. Costing $105,000, it will be shipped in knocked-down state from New Jersey for installation in the first floor of a six-story research wing now being erected at the hospital.

Campaign to Endow Chair in Biochemistry.—A half-million-dollar campaign to endow a chair of biochemistry in honor of Dr. William S. McEllroy, retiring dean of the University of Pittsburgh School of Medicine, is under way by alumni of the school. Dr. McEllroy will retire as dean June 30 after 41 years of service to the university. He will retain his academic rank as professor of biochemistry and also will serve as an advisor on medical affairs. Dr. John E. Weigel, assistant professor of surgery and general chairman of the campaign, announced that $100,000 of the needed funds already is available from gifts by medical alumni. The remaining $400,000 will be raised principally through personal solicitation by alumni who have volunteered to assist in the campaign. Dr. McEllroy joined the Pitt medical faculty in 1917 and became dean in 1939 after having served as assistant dean from 1921 until that time.

Philadelphia

Dr. Babcock Feted at Surgical Society Dinner.—Dr. W. Wayne Babcock, emeritus professor of surgery, Temple University School of Medicine, was guest of honor at the commemoration of the 50th anniversary of The Babcock Surgical Society, oldest student organization at the school. Among the guests was Dr. David B. Allman, President, American Medical Association, who spoke on "Medical Education." Other guests included Robert L. Johnson, LH. D., president, Temple University; Dr. William A. Steel, emeritus professor of the principals of surgery at Temple and first president of the Babcock Surgical Society; Dr. William N. Parkinson, dean of the Medical School; and Dr. Robert A. Bucher, associate dean. Senior medical student John A. Udall, current president of the honor society, was toastmaster. Dr. Babcock, who served as head of the department of surgery at Temple University School of Medicine from 1903 until his retirement in 1943, was succeeded by Dr. W. Emory Burnett. In 1954, Dr. Babcock was awarded the American Medical Association's Distinguished Service Medal.

Dedicate Hospital for Rehabilitation.—The Magee Memorial Hospital for Convalescents was opened with formal ceremonies March 9. A five-story, air-conditioned, 78-bed building, it will furnish services for the rehabilitation of physically disabled patients of all income groups, races, and religions over the age of 14 years who are residents of metropolitan Philadelphia. The hospital was established with a 7-million-dollar trust fund left by Miss Anna J. Magee. The cost of the hospital and equipment was about 2.5 million dollars; income from the remaining funds will be used to support free and part-pay beds. The hospital is controlled by representatives of 11 general hospitals of the city including the four large medical school hospitals (Hahnemann, Jefferson, Temple, and University of Pennsylvania). Dr. Henry F. Parry is director of the institution.



The recently dedicated Magee Memorial Hospital for Convalescents.

Select New Dean at Jefferson Medical College.—The board of trustees of Jefferson Medical College has named Dr. William A. Sodeman dean of the college, to succeed Dr. George A. Bennett, who died in February. Dr. Sodeman is the Magee Professor of Medicine and head of the department of medicine at Jefferson. He is certified by the American Boards of Internal Medicine and Preventive Medicine. He was previously a member of the executive faculty of the Tulane University Medical College, New Orleans, and a professor of medicine at the University of Missouri Medical School, Columbia. Dr. Sodeman is a past-president of the American Society of Tropical Medicine.

"American Way" Tour for Foreign Physicians.—Physicians from 34 foreign countries who are furthering their medical education at the University of Penn-

sylvania's Graduate School of Medicine got an intimate look at the "American way" on a special tour-trip to Wilmington, Del., and vicinity April 12. They were guests of the E. I. DuPont de Nemours Company for a day of orientation and sight seeing. The group visited Longwood Gardens for a luncheon where they were joined by American scientists who came from many of the countries represented by the students. They visited the Hagley museum followed by a ride around the 19th century powder yards and a brief inspection of the DuPont Company experimental station. The Wilmington trip is one of a series of four special orientation programs being sponsored by the Junior League of Philadelphia in cooperation with a faculty committee of the Graduate School of Medicine under the chairmanship of Dr. Irwin H. Breslow.

Institute for Cancer Research.—A statement released by the Institute for Cancer Research for clarification of its name states that "The Institute for Cancer Research and The Lankenau Hospital Research Institute have been the combined titles by which the institute has been known during the past decade. When the institute was first formed in 1925 it was named the Lankenau Hospital Research Institute. In 1944 a separate nonprofit corporation was organized, and thereafter, The Institute for Cancer Research and The Lankenau Hospital Research Institute, known by their joint names, were operated as a unit. To avoid confusion between the institute and the separate program now being organized at The Lankenau Hospital for the purpose of investigation in a number of fields under the direction of Dr. Kaare Rodahl, the name, The Lankenau Hospital Research Institute, shall be abandoned and will no longer be used in conjunction with the name of The Institute for Cancer Research. The Institute for Cancer Research will continue to function under its new director, Dr. Timothy R. Talbot Jr., and Dr. Stanley P. Reimann will continue as director emeritus."

Personal.—Dr. Bernard P. Widmann, director of Philadelphia General Hospital's radiology department, has received the Shaffrey Award of St. Joseph's College Medical Alumni Association, "in recognition of exemplary service rendered to local hospitals and for scientific contributions in the field of radiology."——Dr. Carroll F. Burgoon Jr., chairman, department of dermatology and syphilology, Hahnemann Medical College, has been appointed medical director of the Skin and Cancer Hospital of Philadelphia.——Joseph V. Swintosky, Ph.D., of the Smith, Kline & French Laboratories, has been named by the American Pharmaceutical Association as the 1958 recipient of the Ebert Prize, awarded "for the best original research paper published in the journals of the American Pharmaceutical Association during each preceding year." Prior to 1953, Dr. Swintosky was assistant professor of pharmacy at the University of Wisconsin, Madison.——Dr. John F. Stouffer, retired chief of psychiatry at the city-owned Philadelphia General Hospital, has received the Junior Chamber of Commerce's "Buck Sawyer Award," named for Philadelphia's first managing director, Robert W. Sawyer, who died in February, 1955. Dr. Stouffer, whose 34-year career as chief of the hospital's neuropsychiatric department spanned nearly the entire history of the 268-bed unit, retired Feb. 1.

WEST VIRGINIA

Alumni Meeting in Morgantown.—The annual meeting of the Alumni Association of the West Virginia University School of Medicine will be held at the new Medical Center in Morgantown June 1, 2 p. m., with the president, Dr. John F. McCuskey, of Clarksburg, presiding. Dr. Ralph E. Knutti, of the Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Washington, D. C., will speak on "The Program of the Institute as they Affect Practicing Physicians." Gordon R. McKinney, Ph.D., associate professor of pharmacology at the university, will present "Studies in the Metabolism of Leucocytes: Implications in Health and Disease." Dr. Pat A. Tuckwiller, of Charleston, is vice-president of the association, and Dr. Clark K. Sleeth, of Morgantown, is secretary-treasurer.

Personal.—Dr. Page H. Seekford, who has for the past several years engaged in industrial and general practice at Nellis, Seth, and Prenter, in Boone County, has accepted appointment as director of the Kanawha–Charleston Health Department, effective March 1. He will succeed Dr. Ritchie A. Ireland, of Charleston, who has been serving as acting director since early in December, succeeding Dr. Leon A. Dickerson, who resigned to accept appointment as director of disease control, State Department of Health.——Dr. Harry E. Handley, of New York City, has been appointed deputy director of the West Virginia Department of Health. He assumed his new duties on March 1. Dr. Handley is currently serving as a public health associate for the Commonwealth Fund in New York City.

GENERAL

Plan Tour to Israel.—The American Physicians Fellowship, Inc. for the Israel Medical Association is sponsoring an all-inclusive tour to Israel for the fourth World Medical Assembly of the Israel Medical Association to be held in Tel Aviv, Haifa, Jerusalem, Aug. 12-24. The group will depart from New York via El Al Israel Airlines Aug. 9, and will leave Israel Aug. 24. For details contact the National Office at 1330 Beacon St., Brookline 46, Mass.

Traffic Deaths Decrease for March.—Cities led the way to the lowest March traffic death toll since 1955, the National Safety Council has reported. The March tally of deaths was 2,630 for the nation, a reduction of 9% from the March level a year ago. Cities of 10,000 population or more achieved a 14% reduction. Traffic deaths totaled 2,890 in March last year, the council said. In 1955, the toll was 2,602. March was the fifth month in a row and the 15th out of the last 16 in which traffic deaths totaled the same or fewer than in the corresponding months of the previous year. For the first quarter of the year, the death toll was 7,730—down 6% from last year's 8,250.

Grant for Study of Mental Hospital Programs.—The Southern Regional Education Board has received a grant which will enable staff members of Southern mental hospitals to observe new or unusual programs in other hospitals, starting June 1. The grant was made by the National Institute of Mental Health in the amount of $42,000 for the 1958-1959 period and $48,000 for the 1959-1960 period. The grants to hospital staff members will vary with each request and will be made according to the need in each case but will not exceed $500. Applications must be made to the board through the head administrator of the applicant's hospital.

Foundation for Research in Parkinson's Disease.—Announcement has been made of the establishment of a foundation for research into the cause and cure of Parkinson's Disease and related disorders. The officers of the Parkinson's Disease Foundation, Inc., include Mr. William Black, president; Dr. Edgar A. Lawrence, treasurer; Mr. Lawrence Valenstein, secretary; Dr. H. Houston Merritt, chairman, research advisory board; and Dr. Melvin D. Yahr, medical director. The offices of the foundation are at 125 E. 50th St., New York 22. Grants will be made to assist the work of investigators in this field. Application blanks are now available at the offices of the foundation and, when submitted, they should be addressed to Dr. Yahr.

International Surgeons Elect Officers.—Prof. Dr. Raffaele Paolucci diValmaggiore, head, surgical clinic, University of Rome, Italy, has been chosen president-elect of the International College of Surgeons, to be installed in September, when Dr. Henry W. Meyerding, Rochester, Minn., will become president to succeed Prof. Dr. Carlos Gama, of Sao Paulo, Brazil. Other international officers elected are: first vice-president, Dr. Lyon H. Appleby, Vancouver, B. C., Canada, and the following vice-presidents from the U. S.: Drs. Alexander Brunschwig, New York City; Edward L. Compere, Chicago; Arnold S. Jackson, Madison, Wis.; and Francis L. Lederer, Chicago. International secretary general is Dr. Max Thorek, Chicago; treasurer, Dr. Clement L. Martin, Chicago, and executive director, Dr. Ross T. McIntire, Chicago.

Scientific Tape Recordings Available.—A catalog of tape-recorded scientific lectures by recognized medical authorities has been prepared under the auspices of the Commission on Medical Education and Licensure of the Indiana State Medical Association. These tapes, recorded at 3¾ IPS, include medical forums, and such subjects as cardiovascular and peripheral-vascular diseases, cancer, obstetrics and gynecology, psychiatry, pediatrics, and treatment. Instructions for loan or purchase of tapes by members and nonmembers of the state society can be found on the first page of the catalog entitled "Learning Through Listening." Copies of the catalog and tapes are available from: Indiana State Medical Association, 1021 Hume Mansur Building, Indianapolis 4, Ind.

Nutritionists Receive Awards.—At a dinner commemorating the 25th anniversary of the founding of the American Institute of Nutrition, Lemuel D. Wright, Ph.D., professor of nutrition, Cornell University, Ithaca, N. Y., was awarded the 1958 Borden Award in Nutrition ($1,000 and a gold medal), and The Osborne and Mendel Award ($1,000) was presented to Dr. Paul Gyorgy, pediatrician-in-chief at the Hospital of the University of Pennsylvania, Philadelphia. Before joining the staff of Cornell, Dr. Wright was a research associate at Merck, Sharp and Dohme Research Laboratories. Dr. Gyorgy, discoverer of riboflavin and of vitamin B_6, is a native of Hungary. The Borden Award in Nutrition is given annually by the Borden Company Foundation, Inc.; the Osborne and Mendel Award by the Nutrition Foundation, Inc.

Fellowships in Industrial Psychiatry.—To meet the need for industrial psychiatrists in major American industrial firms, the Carnegie Corporation of New York has granted support for Cornell fellowships of two years duration. One academic year is spent in residency at Cornell's New York State School of Industrial and Labor Relations, with individualized course work in industrial human relations, personnel problems, preventive mental health programs, etc. The second year is spent in a supervised internship at a selected business or industrial company. The total program is approved as one-year residency in psychiatry. The stipend is $5,250 for the first year and, with satisfactory performance, $5,750 for the second year. To be eligible for the fellowships applicants must have completed a minimum of two years residency in psychiatry. For information write

to Dr. Fred T. Burling, New York State School of Industrial and Labor Relations, Cornell University, Ithaca, N. Y.

Card for Patients on Anticoagulant Therapy.—An "emergency" identification card for the protection of patients on long-term anticoagulant therapy is now available to physicians from the American Heart Association and its affiliates. The card, designed as a wallet insert, was developed as a result of requests from physicians seeking to protect their patients on anticoagulants in case of accident, dental surgery, or other treatment that may induce bleeding. It points out that the bearer "is being treated with anticoagulants which slow down clotting of the blood." In case of emergency—bleeding, injury or illness—the card advises that a doctor be called, since the patient may require an antidote. The card has space to indicate the kind of anticoagulant prescribed and the patient's blood type. Physicians may obtain samples of the card from their local heart association or from the American Heart Association, 44 E. 23rd St., New York City.

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Rehabilitation Fellowships for Venezuelans.—A program to supplement Venezuela's medical facilities and techniques for rehabilitating the crippled and handicapped has been announced by Mr. Percy C. Spencer, LL.B., president of Sinclair Oil Corporation, through its Venezuelan affiliate, Sinclair Venezuelan Oil Company. Fellowships will be established to enable a selected group of Venezuelan doctors, nurses, physical therapists, social workers, and prosthetic technicians to obtain further training and experience at the Institute of Physical Medicine and Rehabilitation, New York University–Bellevue Medical Center and other rehabilitation centers in the United States. The program will be administered by the World Rehabilitation Fund and its president, Dr. Howard A. Rusk, chairman, department of physical medicine and rehabilitation at the medical center. Dr. Rusk has helped establish rehabilitation programs in some 36 countries, principally through the International Society for the Welfare of Cripples, a nongovernmental organization.

Northwest Meeting of Plastic Surgeons.—The 1958 meeting of the Pacific Northwest Society of Plastic and Reconstructive Surgery will be held May 23-24 in Tacoma, Wash. Three movies are planned: "Control of Hemorrhage," presented by Dr. Walter S. Brown, Seattle, and "Mammaplasty" and "Motivation in Overcoming Handicaps," presented by Dr. David E. Sullivan, Spokane, Wash. Program topics and speakers include:

Homograft Survival, Dr. Cyrus G. Pow, Vancouver, British Columbia, Canada.
Ectopic Salivary Tumor of Upper Lip, Dr. Robert J. Cowan, Vancouver, B. C.
Trismus, Dr. Emile J. Badre, Vancouver, B. C.
Reduction of the Hypertrophied Breast, Dr. Charles E. Gurney, Portland, Ore.
Complications in the Care of Major Burns, Dr. Edward E. Wayson, Portland, Ore.
Correction of the Deformed Mucocutaneous Angle, Dr. Adalbert G. Bettman, Portland, Ore.

For information write the Pacific Northwest Society of Plastic and Reconstructive Surgery, 419 Mayer Building, Portland 5, Ore.

Decrease in Mental Patients.—Despite an increase in admissions, the population of U. S. mental hospitals continued to decline in 1957, a survey released by the American Psychiatric Association and the National Association for Mental Health has disclosed. It marked the second year of downtrend in mental hospital rolls after a 25-year climb. Admissions during 1957 increased by 5.6% while discharges increased by 9.2%. With other factors, including a 2.4 reduction in mental hospital deaths, the net drop in population amounted to one half of one per cent in state, county, and veterans' mental hospitals, sustaining a "turning point" which started in 1956. During 1957, expenditures per patient were increased from $3.27 a day to $3.64 a day. Full-time employes in public mental hospitals rose from 153,715 to 162,885, an increase of 6%. Last year 23 states increased their appropriations per patient by more than 10% and 12 increased the amount by more than 15%. Kentucky spent 57.5% more per patient than in the previous year, bringing up the figure to $3.25 a day, and increased the number of full-time personnel per 100 patients by 42.3%, or from 21.3 employees per 100 patients to 30.3.

Plague in Rodents.—Mr. F. M. Prince, Public Health Service San Francisco Field Station, has reported the isolation of *Pasteurella pestis* from the following specimens collected in Klamath County, Oregon:

Specimen 663—One *Microtus montanus* (field mouse) found dead, Jan. 26, five miles northwest of Klamath Falls.
Specimen 688—One *M. montanus* found dead, Jan. 26, six miles northwest of Klamath Falls.
Specimens 872 and 893—*Citellus beldingi oregonus* (ground squirrel), one found dead and one trapped, March 6, twelve miles east of Klamath Falls.

The recent isolations were from rodents collected in an investigation of an explosive buildup of the *Microtus* population which was first noted last fall in Klamath County. The density of this population reached as high as 10,000 per acre in some areas and remained at an abnormally high level during the past winter. Of a limited number of samples of mice a high proportion was found to have tularemia. Only one confirmed case of human plague has ever been reported in Oregon. This was in a sheepherder employed in Lake County which is adjacent to Klamath. He developed plague and died in 1934. A suspect case in another sheepherder occurred in 1943 in Harney County.

Prevalence of Poliomyelitis.—According to the National Office of Vital Statistics, the following number of reported cases of poliomyelitis occurred in the United States, its territories and possessions in the weeks ended as indicated:

Area	April 26, 1958 Paralytic Type	April 26, 1958 Total Cases	April 27, 1957 Total
New England States			
Maine	..	..	..
New Hampshire	..	..	..
Vermont	..	..	..
Massachusetts	..	..	..
Rhode Island	..	..	..
Connecticut	..	..	..
Middle Atlantic States			
New York	..	..	..
New Jersey	..	..	..
Pennsylvania	..	..	1
East North Central States			
Ohio	..	..	1
Indiana	..	1	..
Illinois	..	..	..
Michigan	1	1	1
Wisconsin	..	..	1
West North Central States			
Minnesota	..	..	..
Iowa	..	..	..
Missouri	..	..	..
North Dakota	..	..	1
South Dakota	..	..	..
Nebraska	..	..	1
Kansas	..	1	1
South Atlantic States			
Delaware	..	..	..
Maryland	..	..	..
District of Columbia	..	..	..
Virginia	..	..	1
West Virginia	..	..	..
North Carolina	..	..	..
South Carolina	..	..	1
Georgia	..	..	..
Florida	..	1	4
East South Central States			
Kentucky	1	3	2
Tennessee	1	1	1
Alabama	..	..	1
Mississippi	..	1	..
West South Central States			
Arkansas	..	..	1
Louisiana	..	..	3
Oklahoma	..	..	..
Texas	2	4	6
Mountain States			
Montana	..	..	..
Idaho	..	..	1
Wyoming	..	..	..
Colorado	..	..	1
New Mexico	..	..	1
Arizona	..	..	3
Utah	..	..	1
Nevada	..	..	..
Pacific States			
Washington	..	..	..
Oregon	..	..	1
California	1	1	13
Territories and Possessions			
Alaska	..	..	..
Hawaii	2	2	..
Puerto Rico	..	..	..
Total	8	16	48

Nuclear Medicine Society Meeting.—The Society of Nuclear Medicine will hold its fifth annual meeting in Los Angeles June 19-21, according to Dr. Marshall H. Brucer, chairman, Medical Division, Oak Ridge Institute of Nuclear Studies and president of the society. Subjects of the papers deal with diagnostic, therapeutic, and fundamental research implications or applications. Chairman of the program committee is Granvil C. Kyker, Ph.D., chief of laboratory research at the ORINS Medical Division. The formal sessions will also include four instructional courses that will be offered on two days and will deal with thyroid-uptake calibration, measurement of mixtures of radioisotopes, measurement of total exchangeable electrolyte, and medical application of a five-watt aerojet reactor. The meeting will include tours of Los Angeles nuclear medical facilities, a session on the training of physicians in the use of radioisotopes, and scientific and commercial exhibits. A series of 37 small midget exhibits designed to supply a physician with the preclinical information he needs before using radioisotopes is planned. Information is available from the secretary of the society, Dr. Robert W. Lackey, 452 Metropolitan Building, Denver.

Meeting of Chest Physicians in San Francisco.—The 24th annual meeting of the American College of Chest Physicians will be held June 18-22 at the Fairmont Hotel, San Francisco. Seminars on pulmonary disease (medical) and cardiology (surgical) are planned for June 8, with question-and-answer periods following each lecture. The third Louis Mark Memorial Lecture, "The Individual Man and Medicine," will be given by Dr. John B. deC. M. Saunders, dean, University of California School of Medicine, San Francisco. A clinical cardiac conference moderated by Dr. John J. Sampson, 28 "fireside conferences," and the following forums are scheduled: Basic Research in Diseases of the Chest: (1) Pulmonary, (2) Cardiac, and Pulmonary and Cardiovascular Effects of Smoking. Symposiums on tuberculosis, clinical cardiology, idiopathic interstitial fibrosis of the lung, biologic effects of radioactive exposure on the lungs, effects of air pollution on the lungs, and congenital heart disease are arranged. Round-table luncheons will be held June 20-22. A program of ladies' activities is planned, and the annual president's banquet will be held June 21, 7:30 p. m. For information write the American College of Chest Physicians, 112 E. Chestnut St., Chicago 11.

Meeting of Association for the Deaf.—The 23rd summer meeting of the Alexander Graham Bell Association for the Deaf will be held June 22-27 in Pittsburgh. Speakers at the five-day program will include S. Richard Silverman, Ph.D., director, Central Institute for the Deaf; Mr. Louis M. DiCarlo, executive director, Gordon D. Hoople Hearing & Speech Center, Syracuse University; Freeman McConnell, Ph.D., director, Bill Wilkerson Hearing & Speech Center, Vanderbilt University; and Mr. Robert Frisina, director, Hearing and Speech Center, Gallaudet College. The Rev. Fr. Bernard

Tervoort, of the School for the Deaf, St. Michielsgestel, The Netherlands, will also speak. Of special interest to parents will be a one-day session devoted to the organization of the newly formed parents' section of the association. Under the chairmanship of William G. Hardy, Ph.D., director, Hearing and Speech Center, Johns Hopkins Hospital, Baltimore, parents will elect officers and plan action to improve the education of deaf children. The Alexander Graham Bell Association for the Deaf is an organization to promote teaching of speech and lipreading to the deaf.

FOREIGN

Congress on Child Psychiatry.—The fourth International Congress for Child Psychiatry, under the auspices of the Portuguese Government, will be held June 15-20 at the Medical School Hospital of Santa Maria, Lisbon, Portugal. Official languages will be French, English, German, and Portuguese with simultaneous translation provided in the plenary sessions. Subject for the congress is "The Psychological Problems of Children Between the 6th and the 10th Year of Age," and will be dealt with under the following division headings: (1) emotional lack in children between 6 and 10, (2) teamwork in child psychiatry, (3) the formation of child psychotherapists, (4) psychotherapeutic methods, (a) infantile analyses, (b) individual psychotherapy. Afternoon discussion groups of limited membership will consider the following:

Clinical problems in relation to psychotherapeutic methods.
External relations of the child guidance team (cooperation with pediatrists, schools, jurisdictional services for minors, social services, etc.; methods of preventive mental hygiene).
Diagnostic terminology.
Institutions for the treatment of irregular children.
Group therapy for children.
Relations of children with their families.
Psychotherapy and psychosomatic problems.
Emotional problems and the psychological care of sick children.
Children and school.

Fees are $15 for associate members and $5 for accessory members. For information write the General Office, Instituto A. A. Da Costa Ferreira, Travessa Terras Santana, 15, Lisbon, Portugal.

Congress on Allergology in Paris.—The third International Congress of Allergology will be held in the New Medical School, Paris, Oct. 19-25, sponsored by the International Association of Allergology, under the presidency of Dr. Samuel M. Feinberg, Chicago, and by invitation of the French Allergy Association. The program will include symposiums on asthma and emphysema, physic-chemical properties of allergic antibodies, recent advances in phases of clinical allergy, biochemical aspects in hypersensitivity, a round-table conference on autoimmune reactions, a discussion of allergy management and problems in different parts of the world (including socioeconomic aspects), and a demonstration of special techniques in clinical and experimental allergy. Participants will include Sir Henry Dale and Pasteur Vallery-Radot. For information write Dr. Bernard Halpern, 197 Boulevard St., Germain, Paris VII°, France. A post-convention tour is also being planned. The social aspects of the Congress will include a reception and party at the Louvre Museum, an evening at the opera (ballet), conducted tours, and a party at the Medical School.

EXAMINATIONS AND LICENSURE

EDUCATIONAL COUNCIL FOR FOREIGN MEDICAL GRADUATES, INC.

Educational Council for Foreign Medical Graduates, Inc.: The American medical qualification examination to be given henceforth twice a year for foreign medical graduates. Medical Schools in the United States and Foreign Countries, Sept. 23. Final date for filing application is June 23. Executive Director, Dr. Dean F. Smiley, 1710 Orrington Ave., Evanston, Illinois.

NATIONAL BOARD OF MEDICAL EXAMINERS

NATIONAL BOARD OF MEDICAL EXAMINERS: *Written. Parts I and II.* All medical centers in the United States and Canada, June 17-18. Sec., Dr. John P. Hubbard, 133 S. 36th St., Philadelphia.

BOARDS OF MEDICAL EXAMINERS

ALABAMA: *Examination.* Montgomery, June 17-19. Sec., Dr. D. G. Gill, State Office Building, Montgomery 4.

ARIZONA:* *Examination.* Phoenix, July 16-18. *Reciprocity.* Phoenix, July 19. Sec., Dr. Thomas N. Bate, 826 Security Bldg., Phoenix.

ARKANSAS:* *Examination.* Little Rock, June 5-6. Sec., Dr. Joe Verser, Harrisburg.

CALIFORNIA: *Written Examination.* San Francisco, June 16-19; Los Angeles, August 18-21; Sacramento, Oct. 20-23. *Oral Examination.* San Francisco, June 14; Los Angeles, August 16; San Francisco, November 15. *Oral and Clinical Examination for Foreign Medical School Graduates.* San Francisco, June 15; Los Angeles, August 17; San Francisco, November 16. Sec., Dr. Louis E. Jones, 1020 N Street, Sacramento.

COLORADO:* *Examination and Reciprocity.* Denver, June 10-11. Exec. Sec., Mrs. Beulah H. Hudgens, 715 Republic Bldg., Denver 2.

CONNECTICUT:* *Examination.* Hartford, July 8-10. Sec., Dr. Creighton Barker, 160 St. Ronan St., New Haven.

DELAWARE: *Examination and Reciprocity.* Dover, July 8-10. Sec., Dr. Joseph S. McDaniel, Professional Bldg., Dover.

FLORIDA:* *Examination.* Miami, June 29-July 1. Sec., Dr. Homer L. Pearson, 901 N. W. 17th St., Miami.

GEORGIA: *Examination.* Atlanta and Augusta, June 11-12. *Reciprocity.* Atlanta, June 13. Sec., Mr. C. L. Clifton, 224 State Capitol Bldg., Atlanta.

IDAHO: *Examination.* Boise, July 14-16. Exec. Sec., Mr. Armand L. Bird, 364 Sonna Bldg., Boise.

ILLINOIS: *Written Examination.* Chicago, July 7-11. *Oral*

Reciprocity Examination. Chicago, July 11. Supt. of Regis., Mr. Frederic Selcke, Capitol Bldg., Springfield.

INDIANA: *Examination.* Indianapolis, June 18-20. Exec. Sec., Miss Ruth V. Kirk, 538 K. of P. Bldg., Indianapolis.

IOWA:* *Examination.* Iowa City, June 16-18. Exec. Sec., Mr. Ronald V. Saf, State Office Bldg., Des Moines 19.

KANSAS:* *Examination.* Kansas City, June 13-14. Sec., Dr. F. J. Nash, New Brotherhood Bldg., Kansas City.

KENTUCKY: *Written Examination.* Louisville, June 9-11. Sec., Dr. Russell E. Teague, State Board of Health, Louisville 2.

LOUISIANA: *Examination and Reciprocity.* New Orleans, June 5-7. Sec., Dr. Edwin H. Lawson, 930 Hibernia Bank Bldg., New Orleans.

MAINE: *Examination.* Augusta, July 8-10. *Reciprocity.* Augusta, July 8. Sec., Dr. Adam P. Leighton, 142 High St., Portland.

MARYLAND: *Examination.* Baltimore, June 17-20. Sec., Dr. Frank K. Morris, 1211 Cathedral St., Baltimore 1.

MASSACHUSETTS: *Examination.* Boston, July 15-18. Sec., Dr. Robert C. Cochrane, Room 37 State House, Boston.

MICHIGAN:* *Examination.* Ann Arbor and Detroit, June 9-11. Sec., Dr. E. C. Swanson, 118 Stevens T. Mason Bldg., West Michigan Ave., Lansing 8.

MINNESOTA:* *Examination.* Minneapolis, June 17-19. *Reciprocity.* Minneapolis, June 19. Sec., Dr. F. H. Magney, 230 Lowry Medical Arts Bldg., St. Paul 2.

MISSISSIPPI: *Examination.* Jackson, June 23-24. *Reciprocity.* Jackson, June 25. Asst. Sec., Dr. R. N. Whitfield, Old Capitol Bldg., Jackson 113.

MISSOURI: *Examination.* St. Louis, May 30-31. Ex. Sec., Mr. John A. Hailey, Jefferson City.

MONTANA: *Examination and Reciprocity.* Helena, Oct. 7. Sec., Dr. Thomas L. Hawkins, 555 Fuller Ave., Helena.

NEBRASKA:* *Examination.* Omaha, June 16-18. Sec., Mr. Husted K. Watson, Room 1009, State Capitol Bldg., Lincoln 9.

NEVADA:* *Examination and Reciprocity.* Reno, June 3. Sec., Dr. G. H. Ross, 112 No. Curry St., Carson City.

NEW HAMPSHIRE: *Examination.* Concord, Sept. 10-13. *Reciprocity.* Concord, Sept. 10. Sec., Dr. Mary M. Atchison, Room 101, 61 South Spring St., Concord.

NEW JERSEY: *Examination.* Trenton, June 17-20. Sec., Dr. Patrick H. Corrigan, 28 W. State St., Trenton.

NEW YORK: *Examination.* Albany, Buffalo, New York City and Syracuse, June 24-26. Sec., Dr. Stiles D. Ezell, 23 S. Pearl St., Albany.

NORTH CAROLINA: *Examination.* Raleigh, June 16-19. *Reciprocity.* Raleigh, June 17 and Blowing Rock, July 25. Asst. Sec., Mrs. Louise J. McNeill, Professional Bldg., Raleigh.

NORTH DAKOTA: *Examination.* Grand Forks, July 9-11. *Reciprocity.* Grand Forks, July 12. Sec., Dr. C. J. Glaspel, Grafton.

OHIO: *Examination.* June 19-21, Sec., Dr. H. M. Platter, 21 West Broad St., Columbus 15.

OKLAHOMA:* *Examination.* Oklahoma City, June 3-4. Sec., Dr. E. F. Lester, 813 Braniff Bldg., Oklahoma City.

OREGON:* *Examination.* Portland, July 16-17. Exec. Sec., Mr. Howard I. Bobbitt, 609 Failing Bldg., Portland 4.

PENNSYLVANIA: *Examination.* Philadelphia and Pittsburgh, July 8-10. Acting Sec., Mrs. Marguerite G. Steiner, Box 911, Harrisburg.

RHODE ISLAND:* *Examination.* Providence, June 26-27. Administrator of Professional Regulation, Mr. Thomas B. Casey, 366 State Office Bldg., Providence.

SOUTH CAROLINA: *Examination.* Columbia, June 24-25. Sec., Dr. H. E. Jervey, 1329 Blanding St., Columbia.

SOUTH DAKOTA:* *Examination.* Rapid City, August 12-13. Exec. Sec., Mr. John C. Foster, 300 First National Bank Bldg., Sioux Falls.

TENNESSEE:* *Examination.* Memphis, Madison and Dunlap, June 11-12; Nashville, June 3-4. Sec., Dr. H. W. Qualls, 1635 Exchange Bldg., Memphis.

TEXAS:* *Examination and Reciprocity.* Fort Worth, June 23-25. Sec., Dr. M. H. Crabb, 1714 Medical Arts Bldg., Fort Worth 2.

UTAH: *Examination.* Salt Lake City, July 9-11. Director, Mr. Frank E. Lees, 324 State Capitol Bldg., Salt Lake City 1.

VERMONT: *Examination.* Burlington, June 19-21. *Reciprocity.* Burlington, June 19. Sec., Dr. F. J. Lawliss, Richford.

VIRGINIA: *Examination.* Richmond, June 12-14. *Reciprocity.* Richmond, June 11. Address: Board of Medical Examiners, 631 First St., S. W., Roanoke.

WASHINGTON:* *Examination.* Seattle, July 14-16. Administrator, Mr. Thomas A. Carter, Capitol Bldg., Olympia.

WEST VIRGINIA: *Examination and Reciprocity.* Charleston, July 14-16. Sec., Dr. N. H. Dyer, State Office Bldg., No. 5, Charleston.

WISCONSIN:* *Examination.* Milwaukee, July 8-10. Sec., Dr. Thomas W. Tormey, Jr., 1140 State Office Bldg., 1 West Wilson St., Madison.

WYOMING: *Examination and Reciprocity.* Cheyenne, June 2 and Oct. 6. Sec., Dr. Franklin D. Yoder, State Office Bldg., Cheyenne.

ALASKA:* On application in Anchorage and Juneau. Sec., Dr. W. M. Whitehead, 172 South Franklin St., Juneau.

GUAM: *Subject to Call.* Act. Sec., Dr. S. F. Provencher, Agana.

HAWAII: *Examination.* Honolulu, July 14-15. Sec., Dr. I. L. Tilden, 1029 Kapiolani St., Honolulu.

BOARDS OF EXAMINERS IN THE BASIC SCIENCES

ALASKA: *Examination.* Juneau, Nov. 4. Sec., Dr. R. Harrison Leer, Room 204, Alaska Office Bldg., Juneau.

ARIZONA: *Examination.* Tucson, June 17. *Reciprocity.* Tucson, June 27. Sec., Dr. Herman E. Bateman, University of Arizona, Tucson.

ARKANSAS: *Examination.* Little Rock, Oct. 6-7. Sec., Dr. S. C. Dellinger, Zoology Department, University of Arkansas, Fayetteville.

COLORADO: *Examination and Reciprocity.* Denver, Sept. 3-4. Sec., Dr. Esther B. Starks, 1459 Ogden St., Denver 18.

CONNECTICUT: *Examination and Endorsement.* New Haven, June 14. Exec. Asst., Mrs. Regina G. Brown, 258 Bradley St., New Haven 10.

FLORIDA: *Examination.* Miami, June 7. Sec., Mr. M. W. Emmel, Box 340, Gainesville.

IOWA: *Examination.* Des Moines, July 8. *Reciprocity.* Des Moines, July 7. Sec., Dr. Elmer W. Hertel, Waverly.

KANSAS: *Examination.* Kansas City, June 3-4. Sec., Dr. R. E. Stowell, University of Kansas School of Medicine, Kansas City 12.

MINNESOTA: *Examination.* Minneapolis, June 3-4. Sec., Dr. Raymond N. Bieter, 105 Millard Hall, University of Minnesota, Minneapolis.

NEVADA: *Examination.* Reno, June 3. Sec., Dr. Donald G. Cooney, Box 9005, University of Nevada, Reno.

NEW MEXICO: *Examination.* Santa Fe, July 20. *Reciprocity.* Santa Fe, June 26. Sec., Mrs. M. Cantrell, P. O. Box 1522, Santa Fe.

OKLAHOMA: *Examination and Reciprocity.* Oklahoma City, Sept. 26-27. Sec., Dr. E. F. Lester, 813 Braniff Bldg., Oklahoma City.

OREGON: *Examination.* Portland, June 7. Sec., Dr. Earl M. Pallett, Box 5175, Eugene.

SOUTH DAKOTA: *Examination.* Vermillion, June 6-7. Sec., Dr. Gregg M. Evans, 310 E. 15th St., Yankton.

TENNESSEE: *Examination.* Memphis, July 1-2. Sec., Dr. O. W. Hyman, 62 S. Dunlap St., Memphis.

TEXAS: *Examination.* October. Certificates issued by reciprocity and waiver on the first and fifteenth of each month. Sec., Bro. Raphael Wilson, 407 Perry-Brooks Bldg., Austin.

WISCONSIN: *Examination.* Milwaukee, June 7 and Madison, Sept. 19. Sec., Mr. William H. Barber, 621 Ransom St., Ripon.

*Basic Science Certificate required.

DEATHS

Amick, Louis Burton ✱ Sac City, Iowa; Chicago College of Medicine and Surgery, 1908; veteran of World War I; served as health officer; on the staff of the Loring Hospital; died Feb. 22, aged 77, of cardiovascular accident.

Balkema, Walter S. ✱ Sheldon, Iowa; State University of Iowa College of Medicine, Iowa City, 1932; for many years secretary-treasurer of the O'Brien County Medical Society; on the staff of the Community Memorial Hospital, where he died Feb. 4, aged 69, of adenocarcinoma.

Bame, Samuel Rolland ✱ Carey, Ohio; Eclectic Medical College, Cincinnati, 1911; veteran of World War I; died March 17, aged 73, of coronary thrombosis.

Blair, James Albert ✱ Home, Pa.; Jefferson Medical College of Philadelphia, 1923; on the courtesy staff of the Western Pennsylvania Hospital in Pittsburgh; died March 17, aged 65, of coronary occlusion.

Blair, William McBroom ✱ Wharton, Texas; Baylor University College of Medicine, Dallas, 1931; member of the American Trudeau Society; fellow of the American College of Surgeons; past-president of the Wharton County Tuberculosis Association; at one time on the faculty of his alma mater; on the staff of the Caney Valley Hospital, where he died March 14, aged 55, of acute coronary occlusion.

Boylston, Bedford Forrest ✱ Houston, Texas; born in Aiken, S. C., Sept. 25, 1916; Jefferson Medical College of Philadelphia, 1941; on the faculty of the Baylor University College of Medicine; at one time instructor of surgery at the Columbia University College of Physicians and Surgeons in New York City; specialist certified by the American Board of Orthopedic Surgery; president of the Houston Orthopedic Club; member of the American Academy of Orthopaedic Surgeons; fellow of the American College of Surgeons; veteran of World War II; on the staffs of the Jefferson Davis, Methodist, and Veterans Administration hospitals; died in the M. D. Anderson Hospital March 22, aged 41, of cancer.

Brey, Peter Francis ✱ Milwaukee; Milwaukee Medical College, 1910; died in the Milwaukee County Hospital in Wauwatosa, Wis., March 22, aged 79, of pulmonary embolism and bronchopneumonia.

✱ Indicates Member of the American Medical Association.

Brown, Brian Tuck, Sherman, Texas; University of Texas School of Medicine, Galveston, 1918; veteran of World War II; died March 14, aged 64.

Brown, Francis Henry ✱ Des Moines, Wash.; University of Southern California School of Medicine, Los Angeles, 1904; formerly practiced in Seattle and was past-president of the Seattle Academy of Surgery; died March 23, aged 82, of cerebral thrombosis.

Brown, Susan Willard, Cincinnati; Rush Medical College, Chicago, 1922; formerly a medical missionary in China; died March 20, aged 66, of heart disease.

Brown, William Edward ✱ Charlottesville, Va.; Baltimore Medical College, 1908; formerly on the faculty at the University of Virginia Department of Medicine; veteran of World War I; in June, 1944, retired as superintendent and medical director of the Blue Ridge Sanatorium; died in the University of Virginia Hospital March 17, aged 73, of cardiac insufficiency.

Bucher, Louis F., Dayton, Ohio; Rush Medical College, Chicago, 1900; for many years school physician; died in the Miami Valley Hospital March 9, aged 80.

Caldwell, Gene Delmar ✱ Shreveport, La.; University of Nebraska College of Medicine, Omaha, 1930; specialist certified by the American Board of Orthopaedic Surgery; member of the Clinical Orthopaedic Society and American Academy of Orthopaedic Surgeons; fellow of the American College of Surgeons and the International College of Surgeons; chief surgeon for the Shriners Hospital for Crippled Children; chief consultant for the Veterans Administration Hospital; veteran of World War II; died March 11, aged 51, of coronary occlusion.

Campbell, Marvin Bishop, Nashville, Tenn.; Vanderbilt University School of Medicine, Nashville, 1906; veteran of World War I; died March 14, aged 78, of pneumonia.

Caraway, Agnes Burt ✱ Shreveport, La.; Louisiana State University School of Medicine, New Orleans, 1950; formerly member of the Mississippi State Board of Health; died March 12, aged 37, of coronary occlusion.

Carlsen, Edwin Lawrence ✻ Tacoma, Wash.; University of Minnesota College of Medicine and Surgery, Minneapolis, 1906; served on the staff of the Northern Pacific Hospital, where he died March 1, aged 78, of hypernephroma of the right kidney.

Carroll, Francis Matthew ✻ Seattle; Cooper Medical College, San Francisco, 1896; fellow of the American College of Surgeons; veteran of World War I; served as city health officer, coroner, and health commissioner; died March 10, aged 88, of chronic myocarditis, emphysema, and bronchiectasis.

Chadwick, Glenn William ✻ Portland, Ore.; College of Medical Evangelists, Loma Linda and Los Angeles, 1951; member of the California Medical Association; died in the Portland Sanitarium and Hospital March 12, aged 33, of massive gastric hemorrhage due to ulcers.

Chaffin, Rafe Chester ✻ Los Angeles; University of Southern California College of Medicine, Los Angeles, 1907; emeritus professor of gynecology at the College of Medical Evangelists; vice-regent and fellow of the International College of Surgeons; fellow of the American College of Surgeons; member of the senior staff of California Hospital, where he died March 23, aged 75, of acute myocardial infarction.

Claflin, Guy Malverton, Adrian, Mich.; Detroit College of Medicine, 1904; veteran of the Spanish–American War and World War I; served as city health officer; died March 20, aged 84, of circulatory failure.

Coughlin, John Benedict ✻ Durham, N. C.; University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore, 1943; member of the American Society of Anesthesiologists and the Medical Society of the State of Pennsylvania; veteran of World War II; died in the Watts Hospital March 3, aged 40.

Craig, Paul Stuart, Washington, C. H., Ohio; University of Cincinnati College of Medicine, 1929; died in the Mount Carmel Hospital, Columbus, Feb. 21, aged 60, of cerebral hemorrhage.

Cronin, John William ✻ Assistant Surgeon General, U. S. Public Health Service, Washington, D. C.; born in Springfield, Ohio, June 15, 1905; University of Cincinnati College of Medicine, 1933; chief of medical services, U. S. Public Health Service, a post to which he was promoted in 1956, and prior to which he was chief of the division of hospital and medical facilities; from 1947 to 1949 chief, Federal Employees Health Division; executive medical officer of the U. S. Coast Guard Training Station, Sheepshead Bay, N. Y., 1943-1944; medical officer in charge of the U. S. Public Health Service Dispensary in Washington from 1944 to 1947; served as chief surgeon and officer in charge of U. S. Penitentiary Hospital in Leavenworth and Fort Leavenworth, Kan., and Federal Reformatory at El Reno, Okla.; at one time instructor of neurology at the University of Colorado in Denver, lecturer in the school of public health nursing, Catholic University, and lecturer at Georgetown University; fellow of the American Public Health Association, American College of Surgeons, and the American Psychiatric Association; service member of the American Medical Association; member of the Association of Military Surgeons of the United States, American Hospital Association; and the Industrial Medical Association; specialist certified by the American Board of Preventive Medicine; received the honorary degree of doctor of science from Miami University, Oxford, Ohio, June 6, 1955; died March 26, aged 52, following a heart attack.

Crawley, Walter Garlington Jr. ✻ Marietta, Ga.; Emory University School of Medicine, Atlanta, 1927; twice president of the Cobb County Medical Society and vice-president of the Georgia Pediatrics Society; formerly practiced in Lancaster, S. C., and served as director of the Chester County Health Department; died in the Piedmont Hospital, Atlanta, March 22, aged 55, of cancer.

Curry, Ernest Francis ✻ Sagamore, Mass.; Tufts College Medical School, Boston, 1905; medical examiner of Barnstable County; for many years school physician for Sagamore and Bournedale; served as health officer; on the staff of the Cape Cod Hospital in Hyannis; died in the McLean Hospital, Waverly, March 17, aged 81, of cardiovascular and respiratory failure.

Dempsey, Joseph Harry, Cleveland; Western Reserve University Medical Department, Cleveland, 1912; on the staffs of the Booth Memorial Hospital in Cleveland and the Euclid–Glenville Hospital in Euclid, Ohio, where he died March 6, aged 71, of multiple pulmonary infarcts.

Downey, Carl Harris, Salem, Ore.; Willamette University Medical Department, Salem, 1912; died March 5, aged 77.

Duran–Reynals, Francisco, New Haven, Conn.; born in Barcelona, Spain, Dec. 5, 1899; Universidad de Barcelona Facultad de Medicina, Spain, 1925; associated with Rockefeller Institute, New York City, for 10 years, first with the rank of assistant and then with the rank of associate; joined the faculty of the Yale University School of Medicine in 1938 as a research assistant, was promoted to research associate in 1941, and was named lecturer and research associate in microbiology in 1952; did

research on the influence of aging on biological processes; lectured at universities, and medical conferences throughout the United States and in Europe and Canada; died in the Grace New Haven Hospital March 27, aged 58, of cancer.

Dutrow, Howard Victor * Dayton, Ohio; born in Charlesville, Md., Dec. 30, 1880; University of Maryland School of Medicine, Baltimore, 1904; specialist certified by the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Otolaryngology; fellow of the American College of Surgeons; past-president of the Montgomery County Medical Society and the Dayton Academy of Medicine; veteran of World War II; for many years member of the medical department of the Isthmian Canal Commission, advancing to chief of eye, ear, nose and throat clinic, Colon Hospital, Canal Zone; associated with Miami Valley Hospital, where he was formerly chief of staff, St. Elizabeth and Good Samaritan hospitals; died March 17, aged 77.

Geyer, Alfred B. * Medical Director, U. S. Public Health Service, retired, Palos Verdes Estates, Calif.; University of Oregon Medical School, Portland, 1930; service member of the American Medical Association; retired from the U. S. Public Health Service Aug. 1, 1955; member of Admiral Byrd's expedition to the South Pole and was awarded the Third Antarctic Service Expedition Medal for his services as surgeon aboard the expedition ship North Star; died in Carmel March 6, aged 55, of coronary occlusion.

Gilkison, William L. * Loogootee, Ind.; Indiana Medical College, School of Medicine of Purdue University, Indianapolis, 1906; on the staff of the Daviess County Hospital in Washington; died Feb. 11, aged 84, of coronary thrombosis.

Gosman, George Henry Rankin * Colonel, U. S. Army, retired, Arcadia, Calif.; University of Pennsylvania Department of Medicine, Philadelphia, 1898; member of the Massachusetts Medical Society; fellow of the American College of Surgeons; veteran of World War I; entered the medical corps of the U. S. Army in 1901; retired Dec. 31, 1922; held the Distinguished Service Medal and other decorations; died in the Veterans Administration Hospital, Los Angeles, Feb. 3, aged 81, of arteriosclerosis.

Graham, Charles L., Tollesboro, Ky.; Kentucky School of Medicine, Louisville, 1906; served on the staff of the Hayswood Hospital, Maysville; died March 6, aged 83.

Grzybowski, Stanley Theodore, Chicago; Chicago Medical School, 1942; served an internship at St. James Hospital in Chicago Heights, and a residency at the Highland Park (Ill.) Hospital and the Veterans Administration Hospital in Hines, Ill.; veteran of World War II; died March 5, aged 45, of coronary occlusion.

Gunn, William Parker * Janesville, Wis.; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1907; member of the Illinois State Medical Society; veteran of World War I; associated with St. Bernard's and Illinois Central hospitals, Chicago; died March 20, aged 75, of coronary thrombosis.

Haas, Fredrick William, Naco, Ariz.; Southwestern Homeopathic Medical College and Hospital, Louisville, Ky., 1906; died in Warren Jan. 4, aged 79, of congestive cardiac disease.

Henderson, James Paris, Excelsior Springs, Mo.; University Medical College of Kansas City, 1903; served as second vice-president of the Missouri State Medical Association; served on the faculty of his alma mater; veteran of World War I; formerly practiced in Kansas City, Mo., where he was associated with the Kansas City General Hospital; served on the staff of the McLeary Hospital and Clinic; died March 11, aged 79, of acute cardiac dilatation.

Howell, William Wescott, Topsham, Maine; Harvard Medical School, Boston, 1900; practiced in Boston; specialist certified by the American Board of Pediatrics; member of the American Academy of Pediatrics and the Massachusetts Medical Society; died in Portland Feb. 14, aged 84, of aneurysm of the abdominal aorta.

Jones, Harold Wellington * Colonel, U. S. Army, retired, Orlando, Fla.; born in Cambridge, Mass., Nov. 5, 1877; Harvard Medical School, Boston, 1901; for two years resident and house physician in the Children's Hospital, Boston; practiced medicine in St. Louis, where he was associate professor of orthopedic surgery at St. Louis University School of Medicine, 1904-1905; commissioned in the Medical Corps of the U. S. Army in 1906; an honor student at the Army Medical School, where he later served as professor and as secretary of the faculty, 1917-1918; was in command of an ambulance train with Pershing in Mexico in 1916 and of the Beau Désert Hospital Center, near Bordeaux, France in World War I, and later of Tripler General Hospital in Honolulu; was chief of the surgical service at the Fort Sam Houston Hospital; was librarian at the Army Medical Library (now National Library of Medicine) in Washington, D. C., from 1936 until 1943 and director from 1944 to 1946; service member of the American Medical Association; an honorary member of the Cleveland

Medical Library Association; formerly secretary-treasurer of Association of Honorary Consultants to the Army Medical Library; was honorary curator, Osler Library, Montreal, from 1936 to 1946, president, Medical Library Association, 1940-41, editor of the *Bulletin of the Medical Library Association*, 1941-1942; awarded the honorary LL.D. degree by Western Reserve University in 1945; in 1956 received the Marcia C. Noyes Award; was chief delegate to the 9th International Congress of Military Medicine in Bucharest in 1937, and secretary-general of the 10th International Congress in 1939 in Washington and editor of its proceedings; vice-president of the International Congress of Air Relief in Bucharest in 1937; delegate in 1937 to the Geneva Convention of the International Hague and Geneva–Red Cross Societies; decorated by France (twice), Rumania, Poland, Mexico, and the United States (Legion of Merit in 1945); fellow of the American College of Surgeons and the American Association for the Advancement of Science; honorary member of the Mexican Association of Military Surgeons; edited the "New Gould Medical Dictionary"; for several years chief editor of the medical section of the "Encyclopedia Americana"; died suddenly April 5, aged 80.

Jones, Isaac Newton, Greensboro, Ala., Birmingham Medical College, 1909; member of the Medical Association of the State of Alabama; served as county health officer; died Feb. 26, aged 74.

Koenig, Charles Albert ✦ Woodville, Pa.; St. Louis University School of Medicine, 1911; served as assistant professor of psychiatry at the University of Pittsburgh School of Medicine; specialist certified by the American Board of Psychiatry and Neurology; member of the American Psychiatric Association; veteran of World War I; for many years clinical director of the Woodville State Hospital; died in St. Mary's Hospital, Riviera Beach, Fla., Feb. 26, aged 73, of pneumonia and diabetes mellitus.

Levison, Louis A. ✦ Toledo, Ohio; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1903; specialist certified by the American Board of Internal Medicine; fellow of the American College of Physicians; associated with Toledo Hospital and St. Vincent's Hospital, where he died March 10, aged 77, of virus pneumonia and hypertensive heart disease.

Lewis, Walter Warren, Marvell, Ark.; University of Tennessee College of Medicine, Memphis, 1914; died in Helena (Ark.) Hospital Jan. 4, aged 69.

Magee, David Miller Pomfret, Marianna, Fla.; University of Pennsylvania Department of Medicine, Philadelphia, 1906; died March 4, aged 73, of pulmonary edema, bronchopneumonia, and congestive heart failure.

Magill, William Henry ✦ Providence, R. I.; Cornell University Medical College, New York City, 1903; fellow of the American College of Surgeons; served on the medical draft board during World War I; formerly chief medical examiner in Rhode Island and for many years Providence medical examiner; associated with Rhode Island and St. Joseph's hospitals; died March 12, aged 87.

Main, Robert E., Vernon, Texas; St. Louis College of Physicians and Surgeons, 1898; died Feb. 5, aged 88.

Margulis, Abraham Bernard ✦ Bridgeport, Conn.; Medical School of Maine, Portland, 1920; died in Miami Beach, Fla., March 8, aged 67, of coronary thrombosis.

Mavraides, William Peter ✦ Boston; University of Vermont College of Medicine, Burlington, 1933; certified by the National Board of Medical Examiners; died March 7, aged 54.

McCann, Neal Joseph ✦ Torrance, Calif.; Loyola University School of Medicine, Chicago, 1928; served as president of the Marquette–Alger Counties (Mich.) Medical Society; veteran of World War I; formerly health officer of Ishpeming, Mich.; died March 10, aged 58, of arteriosclerotic heart disease.

Mixter, William Jason ✦ Woods Hole, Mass.; born in 1880; Harvard Medical School, Boston, 1906; member of the founders group of the American Board of Surgery; specialist certified by the American Board of Neurological Surgery; member of the American Surgical Association, International Society of Surgery, American Neurological Association, and the Association for Research in Nervous and Mental Disease; fellow of the American College of Surgeons; past-president of the New England Surgical Society; veteran of World War I; senior civilian consultant for neurosurgery to the Surgeon General during World War II; honorary surgeon at the Massachusetts General Hospital, where he was chief of neurosurgical service; died March 16, aged 77, of carcinoma of the lung.

Moffett, William Thomas, Blue Mound, Ill.; Rush Medical College, Chicago, 1895; veteran of World War I; died in Wauchula, Fla., Feb. 20, aged 90, of acute cardiac failure.

Mugrage, Edward Rosseter ✦ Denver; born in Leadville, Colo., in 1885; University of Colorado School of Medicine, Denver, 1913; professor emeritus of clinical pathology at his alma mater; specialist certified by the American Board of Pathology; member of the College of American Pathologists and the American Society of Clinical Pathologists; fellow of the American College of Physicians; past-president of the Colorado State Medical Society; for many years secretary-treasurer of the Medical Alumni Association of the University of Colorado School of Medicine; associated with Swedish National Sanatorium in Englewood, St. Luke's Hospital, National Jewish Hospital, Children's, Denver General, Mercy, and St. Joseph's hospitals; died in the Colorado General Hospital March 4, aged 72, of acute enterocolitis.

Tallman, Ralph LaRue ✦ Chicago; Loyola University School of Medicine, Chicago, 1928; a member of the board of governors of South Shore Hospital; died March 20, aged 59.

Taylor, Cornelius John ✦ Bangor, Maine; Medical School of Maine, Portland, 1911; served as medical examiner for Penobscot County; for many years medical examiner for the Metropolitan Life Insurance Company and the New York Life Insurance Company; on the staff of the Eastern Maine General Hospital; died Feb. 18, aged 70, of acute coronary disease.

Taylor, John Mortimer, South Egremont, Mass.; Columbia University College of Physicians and Surgeons, New York City, 1898; died in the Fairview Hospital in Great Barrington March 6, aged 86, of bronchopneumonia.

Taylor, Martin Clever, Pittsburgh; Western Pennsylvania Medical College, Pittsburgh, 1900; an associate member of the American Medical Association; member of the American Academy of Ophthalmology and Otolaryngology; associated with the Southside Hospital; died Feb. 23, aged 80, of pulmonary embolism.

Taylor, Ralph Buren ✦ Columbus, Ohio; Eclectic Medical Institute, Cincinnati, 1898; served as a member of the Ohio State Medical Board; associated with the Grant Hospital, and the Home for Aged; died Feb. 23, aged 84, of arteriosclerosis.

Taylor, Walter Frederick, Keene, N. H.; McGill University Faculty of Medicine, Montreal, Que., Canada, 1914; member of the New Hampshire Medical Society; served as a member of the board of health, and as city and school physician; veteran of World War I; died Feb. 21, aged 70.

Thayer, James Manning ✦ Memphis, Tenn.; University of Tennessee College of Medicine, Memphis, 1954; service member of the American Medical Association; a captain and flight surgeon in the U. S. Air Force; killed Feb. 15, aged 27, in the crash of a transport plane on Mount Vesuvius, outside Naples, Italy.

Thomas, Francis Willard, Columbus, Ohio; Starling–Ohio Medical College, Columbus, 1912; served on the faculty of the Ohio State University College of Medicine; specialist certified by the American Board of Otolaryngology; associated with Grant and Mount Carmel hospitals; died in Palm Beach, Fla., Feb. 18, aged 68, of coronary disease.

Tuttle, George Bass, Arlington, Va.; Washington University School of Medicine, St. Louis, 1894; formerly served in the regular Army; died in the Arlington Hospital Feb. 19, aged 86.

Twente, Julius ✦ Thomasville, Ga.; Rush Medical College, Chicago, 1930; service member of the American Medical Association; medical officer at Veterans Administration Domiciliary; died in the Archbold Memorial Hospital Feb. 4, aged 58.

Walker, William A. ✦ Cairo, Ga.; Louisville (Ky.) Medical College, 1889; served as mayor of Cairo, as a member of the county board of education, and in the Georgia Legislature; died Feb. 20, aged 91.

Webster, Fred Paterson ✦ Portland, Maine; Harvard Medical School, Boston, 1901; member of the American Academy of Pediatrics; at one time professor of pediatrics at the Bowdoin Medical School; on the staffs of the Maine Eye and Ear Infirmary and the Maine General Hospital; died Feb. 26, aged 79, of coronary thrombosis.

Weiss, Rudolf ✦ Cleveland; Medizinische Fakultat der Universitat, Vienna, Austria, 1917; associated with Mount Sinai Hospital; died March 2, aged 66, of myocardial infarction.

Wescott, Clement Plummer ✦ Portland, Maine; Tufts College Medical School, Boston, 1909; served on the staffs of the Mercy and Maine General hospitals; died Feb. 16, aged 79, of heart disease.

Wilson, James Frederick, Washington C. H., Ohio; College of Physicians and Surgeons, Baltimore, 1909; served as secretary of the Fayette County Medical Society; for many years county health commissioner; past-president of the Ohio Federation of Public Health Officials; died in the Mount Carmel Hospital, Columbus, March 4, aged 76, of cerebrovascular thrombosis.

FOREIGN LETTERS

AUSTRIA

Phimosis.—At the meeting of the Society of Pediatrics in Vienna in March Dr. H. R. Jonas emphasized the necessity of differentiating between true phimosis characterized by an abnormal narrowing of the preputial ring and pseudophimosis with an elongation of the prepuce and physiological adhesion of the prepuce to the glans penis. The separation of the preputial adhesions or the stretching of the prepuce in early infancy is in general not advisable. As a rule, the adhesions spontaneously separate in the second or third year of life. The stretching of a contracted and elongated prepuce should be performed with great care but not earlier than between the second and third year. Surgical treatment of a genuine phimosis can be performed as late as the third year of life unless recurrent balanoposthitis or paraphimosis make an early operation necessary. Circumcision with extensive resection of the inner preputial membrane is the operation of choice.

Dr. H. K. Kundratitz stated that surgical treatment of a phimosis is rarely necessary. In most cases stretching the prepuce will correct the condition. He saw no objection to a separation of the adhesions during infancy, since failure to do so might result in balanitis and retention of smegma. Dr. H. W. Lesigang said that the phimosis in nurslings is physiological. Congenital phimosis with a retention of urine rarely occurs, but when present it should be corrected. As long as the flow of urine is free, the condition is harmless. Attempts at stretching of the prepuce by the mother as prescribed by some practitioners is to be condemned for psychological reasons and because of sexual irritation. Inflammations of the prepuce in children from the second to the sixth year of life are mostly caused by friction of the clothes. The friction may cause an inflammatory swelling, especially of a prepuce that has been hypertrophic from birth. In this stage the retraction of the prepuce over the glans is difficult. The usual treatment of such an inflammation will restore normal conditions within a few days.

Symposium on Carcinoma of the Uterine Cervix.—At the meeting of the Society of Physicians in Vienna on March 14 Dr. Antoine said that better results in the campaign against carcinoma of the uterine cervix are due to earlier diagnosis and new therapeutic developments. Three methods for early diagnosis are cytology, colposcopy, and colpomicroscopy. R. Klein and H. Kremer said that malignant epithelial cells are relatively easy to detect in a smear. The findings were accurate in 93.7% of the patients with carcinoma of the uterine cervix and nonevasive carcinoma in their series. Dr. V. Gruenberger said that in 1956 and 1957 of 150 patients with carcinoma of the uterine cervix who were examined by the three methods mentioned, 35 (23.3%) were not suspected of having carcinoma on macroscopic examination. If the doubtful cases are added to those with positive findings of carcinoma, all three methods showed about the same efficacy. Three of these cases were detected by the colpomicroscope alone, and four by cytology alone. In only one case did all three methods fail—an accidental histological detection of subepithelial spread of carcinoma in a patient whose cervix was amputated immediately above the vagina. Of 547 other patients with histologically detected erosions, false-positive findings were obtained in 17 to 20% and a correct diagnosis was made only by biopsy.

Dr. Antoine said that when the results were doubtful the patient should be kept under close observation. A positive result requires biopsy to corroborate the diagnosis. Conization or amputation of the part of the uterine cervix immediately above the vagina combined with a curettage proved to be the most efficacious treatment. Dr. A. H. Dalmrich stated that treatment of the preinvasive carcinoma consisted of high amputation of the cervix or high conization. An extirpation of the uterus would have to follow if all the invaded area was not removed. The Schanta-Wertheim operation can be applied to patients with invasive carcinoma. If operation is still desirable in a patient with advanced carcinoma which has spread to the bladder or rectum, posterior, anterior, or total evisceration must be performed. Drs. E. Picha and K. Weghaupt said that only carcinomas classified in groups 3 and 4 should be irradiated. The standard method includes three insertions which are performed at intervals of two weeks. The first two insertions are vaginal whereby about 80 mg. of radium, radiocobalt, or radiogold is affixed to the front of the cervix. The third insertion (also 80 mg.) is intrauterine. This standard method must be adapted to the individual patient.

Dr. K. Fochem reported that after a radical operation he gives a total of 16,000 r of x-rays in three series. The noninvasive carcinoma (stage 0) is not irradiated postoperatively. If an especially large area has been invaded, up to 12,000 r should be

The items in these letters are contributed by regular correspondents in the various foreign countries.

applied to lateral fields and 2,000 to 3,000 r to a vulvoperineal field. For recurrent cases the body cavity tube, cross fire irradiation, moving irradiation, or grid irradiation may be used. The last-mentioned method proved most valuable because a maximum dosage was least damaging to the skin. In 17 of 30 women with recurrent carcinoma of the uterine cervix who were irradiated, the recurrent tumor disappeared; in 7 the tumor receded slowly, and the rest were therapeutic failures. Dr. J. Spurny said that the absolute five-year cure rate in 312 patients admitted and treated in all stages of the disease amounted to 55.8% with 51% of the patients in an operable condition.

Lupus Erythematosus.—At the meeting of the Society of Physicians in Vienna on March 28, Drs. F. Egghard and H. Braunsteiner reported on five patients with visceral lupus erythematosus. The prodromal phase may last for years; in one patient it lasted eight years. This phase is characterized by few symptoms in most patients, and joint complaints and pleuritis occur most frequently. Joint involvement plays an essential part in the progress of the disease. No major joint deformities occurred in the above-mentioned patients despite a prolonged course. Lupus erythematosus must be differentiated from primary chronic polyarthritis. The characteristic cutaneous changes did not occur in four of the five patients. The diagnosis was based on the L. E. cell test. Four patients became almost completely free of complaints as a result of maintenance therapy with prednisolone. One patient died of renal and pulmonary complications.

Treatment of Edema with Chlorothiazide.—At the same meeting Drs. H. Frischauf and G. Geyer reported on the effect of chlorothiazide, a diuretic related to acetazolamide. Part of the diuretic effect is attributed to suppression of carboanhydrase which may be recognized by the increased elimination of carbon dioxide and the reduction of the titratable acidity in short-term experiments. The increase of sodium excretion occurring after the administration of the diuretic is, however, accompanied by a distinct increase of chloride excretion in contrast to the effect produced by acetazolamide. Chlorothiazide remains effective even if given over a long period.

BRAZIL

Prolapse of Rectum in Childhood.—Prolapse of the rectum in children may be due to conditions which are different from those in adults, such as heavy infestation with intestinal parasites and the position taken during defecation, according to Drs. A. Amorim and A. F. de Camargo (*Maternidade e Infância*, March, 1958). They advocate supporting the natural healing tendencies rather than surgical interference. If operation becomes necessary trauma must be kept to a minimum. In their series of 63 patients 61 made complete recoveries, and 2 left treatment against medical advice.

FRANCE

Mass Production Laboratory.—At the Rothschild Foundation's Laboratory, Suchet has devised a means whereby all the hematological and serologic reactions required can be obtained from a single specimen of blood. One of his centrifuges holds 200 test tubes. He can make 20 different tests with only 1 cc. of blood from the finger. Tests for anemia can be made on 200 people in 10 minutes, and one laboratory technician can perform 1,400 tests a day.

Angina Pectoris.—At a meeting of the French Society of Cardiology M. Blondeau and co-workers reported on the studies of electrocardiographic changes (apart from effort) in 200 patients with angina pectoris of effort, excluding all spontaneous or prolonged attacks and other valvular or hypertensive cardiopathy. The age at which angina pectoris started was between 37 and 71 years. The elapsed time between the onset of angina and the electrocardiographic study was 5 days to 15 years. the tracings showed (1) major anomalies in 56 (bundle-branch block in 13, myocardial infarction in 15, ischemia in 26, and left ventricular hypertrophy in 2); (2) minor anomalies in 82 (flattening of the T wave in 23, flattening of the T wave with dome-shaped ST segment in 9, symmetrical and pointed T waves in 17, and miscellaneous anomalies in 33); and no anomalies in 62. Age and sex did not influence the electrocardiographic patterns but the duration of the disease was an important factor. The maximal electrical deviations were seen in patients with an onset of less than three months. Tracings made after exertion in 38 patients modified the pattern of 13. This was observed more frequently in those with abnormal tracings at rest.

Palfium.—Although the World Health Organization has placed Palfium (2,2-diphenyl-3-methyl-4-morpholino-butyl-pyrrolidine) in the group of poisonous drugs of the same character as morphine, Professor Langeron (*Journal science medicales de Lille*, vol. 76, 1958) vigorously maintains that this drug is not habit-forming. He believes that it is a potent and a true analgesic, suppressing pain rather than masking it. It has no toxic effect on the heart, liver, or kidneys. It provokes minor secondary but frequent reactions (mostly dizziness), but these disappear in time and are rare when the drug is given for severe pain. The dose should be adapted to the individual patient. The drug should be given only under medical supervision.

Cerebral Atrophy in Infantile Chronic Encephalopathy.—Sarrouy and co-workers (*La semaine des hôpitaux de Paris* 34:845, 1958) studied patients with infantile chronic encephalopathy using aeroencephalography to localize areas of cerebral atrophy. False positive diagnoses are often made because of inequality in the thickness of the subarachnoidal space, especially at the level of the frontal lobe; injection of air into the subdural space; and modifications in water metabolism of the cerebral parenchyma. With these reservations in mind it is possible to observe certain changes in the pneumoencephalogram in patients with cerebral atrophy. In the presence of motor disturbances the ventricular dilatation is observed either alone or associated with the cortical sulci, in the shape of irregularities. This is evidence of a subcortical atrophy, most often symmetrical in the case of diplegia and paraplegia and nearly always asymmetrical in the case of hemiplegia. In those patients in whom the psychic or psychomotor disorders prevail there is often a diffuse dilatation of the sulci of the convexity indicating a diffuse cortical atrophy. The pneumoencephalogram is, however, frequently normal. The presence of an obvious cerebellar syndrome associated with the course of an encephalopathy is a radiologically detectable cerebellar atrophy in 90%. In patients with severe encephalopathy, theatrophic changes are usually diffuse, cortical, and subcortical.

Carcinoidosis.—In a symposium on carcinoidosis in *La semaine des hôpitaux de Paris* (34:647-673 [March 4] 1958) Geffroy and Jouanneau stated that the vascular storm characteristic of this disease is probably caused by the discharge of serotonin. Beside the cutaneomucosal, abdominal, and respiratory signs, they observed electroencephalographic manifestations. R. Laumonier and co-workers stressed the absence of lesions in the right side of the heart and the presence of renal changes and cerebral edema in patients with this disease. The histochemical findings showed that silver reduction and argentaffin tests are common to the various types of carcinoid, whether functional or not, whereas yellow fluorescence and the diazo reaction express the functional aptitude of the tumor to elaborating serotonin. Schrub and Geffroy said that the slow development of intestinal carcinoids is no contraindication to the surgical removal of the primary tumor and accessible metastases even though the metastases were widely disseminated. In the presence of carcinoidosis, the use of antagonists to serotonin with a view to preventing the paroxysmal accidents has failed and may even aggravate this disease. Treatment with radioactive colloidal gold was followed by dramatic, but transient, remission.

Community and Health Insurance.—The medical delegates of the national organizations representing cosignatory countries of the European Economic Treaty approved the spirit which presided at the drawing-up of the treaty (*Med. et hyg.* 15:152, 1958). This treaty looked towards establishing harmony between the medicosocial systems and in particular of the various social insurance systems. The physicians representing Western Germany, Belgium, France, Italy, Luxembourg, and Holland, meeting at Luxembourg in January and February, said that the reforms and adjustments of the medicosocial systems should maintain the liberal character of the medical profession but should also conform to the conditions and to the economic and social possibilities of the cosignatory countries. The delegates agreed that (1) the medical profession should keep its liberal character; (2) the patient should have free choice of his physician; (3) the physician should be free to prescribe whatever he believes will benefit his patient; (4) professional secrecy should not be violated; (5) fees should be based on the service given and not on the financial status of the insurance company; (6) the physicians should be represented in all medicosocial organizations; and (7) medical control should be independent of the administrative authorities.

Medical Psychology and Hospitals.—Mr. G. Berger, general director of higher education, at the first conference on medical psychology in March at Rennes announced the creation of an institution of human science (*Med. et hyg.* 15:152, 1958). He said that because the patient's morale is an important factor contributing towards recovery, medical students should be taught the essential elements of psychology. All the speakers stressed the therapeutic value of a comprehensive medical interview, apart from any prescription. Understanding the patient's mental reactions and acting on them has been practiced since Hippocrates. The increasing use of the exact sciences in modern medicine involves the risk of overshadowing the art of medicine, thereby jeopardizing therapeutic results.

Professor Lamache and Dr. Davost deplored the depersonalization of the treatment given in many modern hospitals. This is aggravated by the fact that the patient is deprived of his own clothing and most of his personal belongings and that the visiting hours are often inconvenient for his family. It has been shown that a child separated from his mother has a much longer convalescence than one kept with his parents. Lamache and Davost concluded that visiting of patients in hospital by their families should be encouraged and the psychological and social training of medical students and nurses should be increased. Psychological examination is just as important as roentgenological examination

or blood analysis. The physician should explore the structure of the family environment and the professional and social life of the patient.

ICELAND

Eradication of Echinococcosis.—Dr. N. Dungal (*Nord. med.*, March 27, 1958) stated that in 1890 a law was passed putting a tax of 2 kroner on every dog in the country. Dogs were not to be fed on the entrails of cattle and sheep, and once a year every dog had to be treated with some vermifuge, each county being obliged to provide a building in which all its dogs could be collected for this purpose on a given day. No dog was allowed inside an abattoir, and slaughtering outside an abattoir was forbidden. Hitherto, however, rams were castrated as lambs and were not slaughtered till they were 3 or 4 years old. While at pasture they had thus had ample time in which to become infested. This system has now been abandoned in favor of slaughtering lambs when they are 4 or 5 months old so that the parasite does not have a chance to come to maturity. This change of policy has done more than any other measure to stamp out echinococcosis. Other contributory factors include greatly increased general cleanliness, with improved human habitations to which dogs are not admitted. At the close of the last century, about 25% of the adult population harbored echinococci. In 1956 they were found at 6 of the 279 autopsies performed, and as these cases presumably represented infections dating back a long time, Iceland may now be said to have successfully eradicated the disease.

INDIA

Barium Enema in Intestinal Amebiasis.—Basu and Bhattacharya (*Bulletin Calcutta School of Tropical Medicine*, vol. 5, 1957) studied 84 patients with intestinal amebiasis and diagnosed parasitologically by means of a barium enema. Eight of these were asymptomatic cyst passers, 31 had vague abdominal symptoms, 15 had recurrent diarrhea, and 30 had acute or chronic dysentery; 61 showed suggestive radiological signs after barium enema examination. These included (1) cecal lesions in 27—the cecum did not fill or filled incompletely and this was associated with tenderness and restricted mobility; (2) irregular contour of the colon—this was the most frequent finding, being present in 43; the colon had a moth-eaten appearance or was grossly irregular with a fuzzy outline while fine spicules of the contrast medium projected beyond the colonic outline; the terminal ileum was also irregular in 3 patients; (3) lack of haustration was seen in 5 and irregular haustration in 3; (4) multiple filling defects suggestive of amebic granuloma were seen in 1; and (5) persistent spasm, influx of the barium into the small intestine, and incomplete emptying, as seen in the remaining patients.

These findings were compared with those obtained in 72 patients with nonspecific colitis after a barium enema. Cecal deformity was uncommon in these patients. In a few who showed deformity of the cecum, a past history of dysentery was obtained; while in another, subsequent examination of stools revealed Endameba histolytica. Irregularity of the colon was observed in both conditions. The spiky appearance was more commonly seen in amebiasis but was rarely found in nonspecific colitis. Lack of haustrations was more common in nonspecific colitis. As the radiologic signs were not observed in all patients with amebiasis, although stools examination was positive for E. histolytica, the colonic damage could not be ascertained radiologically in all. In patients in whom radiologic signs were seen, some assessment of the damage could be made. Thus cecal deformities suggested chronic lesions. Spiky appearance was probably indicative of ulceration with or without superimposed localized spasm of the muscularis mucosa. Lack of haustration and irregular haustration suggested chronic inflammation of the colon. Post-evacuation studies of 22 patients in whom emptying was complete showed evidence of chronic colitis such as a disorganized pattern of the mucosa, thickened plicas, and lack of haustrations. Barium enema examination was repeated after treatment in 12 patients. In five the abnormalities had disappeared while others showed persistent fine irregularities. The cecal deformities, whenever present, did not disappear after treatment.

Mongolism in Children.—Manchanda and Guleria (*Indian Journal of Child Health*, vol. 7, February, 1958) came across 35 children with mongolism in a series of 200 mentally retarded children; 21 were below 3 years of age, the youngest being 3 months old and the oldest 15 years. Seven mothers gave birth to normal children after the birth of the mongoloid child; 18 were above 35 years of age; the average age of the mother at the time of the birth of the mongoloid child was about 34 years. There was no history of an attempt to end the pregnancy in any case nor was there any significant illness or accident during the antenatal period. No instance of mongolism was found in other siblings or either parent and none of the 35 children were twins. There was no history of consanguinity. The incidence of some clinical features characteristic of this condition, such as flat occiput, squint, and other ocular anomalies was low in this group as compared with other reports but obliquity of the eyes and hypotonia were present in all cases. Grading of mental retardation revealed imbecility in 50% and idiocy in 30 to 35%; the rest were morons. Congenital ventricular septal defect was suspected

in 3 patients; 16 gave a history of repeated respiratory infections and needed antibiotics. In one child there was evidence of a primary tuberculous complex which was confirmed at autopsy. Histological examination of the brain of this child showed marked atrophy of neurones and increase in cerebral glial tissue. Advanced maternal age was the only possible causative factor observed.

Family Planning.—Launched as an official part of the First Five-Year Plan, the family planning program is gradually gathering momentum. During the Second Plan period, it has been intensified by opening a large number of clinics, urban and rural; providing financial assistance to state governments and voluntary organizations for family planning centers; and extending the training program for different categories of personnel who will implement the program. Research into population problems has also been fostered. Greater efforts are being made to educate the public on the methods of family planning. About $10,500,000 has been allocated to this program in the Second Plan period. The fundamental consideration in this connection is that the population of India is growing at the rate of about 5 million a year and the various programs for economic development envisaged in the Five-Year Plan would be upset by a continuous increase in the population at this rate.

Amodiaquin for Lupus Erythematosus.—P. H. Magnin (*Current Medical Practice*, vol. 11, February, 1958) treated lupus erythematosus with antimalarial drugs. The first to be tried was quinacrine in a series of 23 patients who took 0.3 Gm. by mouth daily. The results were favorable in 17 and the lesions disappeared completely in 8. Because of the side-effects of the drug it was used only topically or by iontophoresis in another group of patients, but the results were not satisfactory. Combined therapy using the drug topically and orally gave better results. The next drug to be tried was chloroquine which was given to 16 patients in a daily dose of 0.5 Gm. The lesions disappeared completely in 8, partially in 6, and in 2 the response was poor. The author then gave 0.4 Gm. of amodiaquin daily to 23 patients. The lesions disappeared completely in 16 and improved in 3. There was only one relapse. Intolerance was infrequent and of little importance. Amodiaquin was thus found to be an active therapeutic agent in the treatment of this disease and in some its results were dramatic. The mechanism of its action is unknown but is probably due to its antiactinic property. Its therapeutic efficiency is equal or even greater than that of other antimalarial drugs used in the treatment of lupus erythematosus. As relapses are frequent, a prolonged follow-up period is necessary.

Treatment of Chorea with Corticotropin.—S. L. Malhotra (*Indian Journal of Child Health*, vol. 7, March, 1958) treated four patients who had chorea with corticotropin. Three had the severe type with involuntary movements that were disabling and one had a mild case. Corticotropin was given by intramuscular injection in two doses, the total daily dose being 10 to 20 units for a period of four to eight days. They were also given 0.6 Gm. of aspirin three times daily and 5 mg. of vitamin K daily by mouth. Clinical classification and progress were based on the clinical features, a dexterity test which consisted of unbuttoning a jacket, and a writing test. The improvement following the injections of corticotropin was dramatic. There was a cessation of involuntary movements and improvement in the dexterity and writing tests. The patients were followed up for periods for 8 to 24 months and the improvement had been maintained, but because of the possibility of remissions, the small number of patients treated, and the absence of suitable controls, no definite conclusion could be drawn.

Industrial Medicine.—At the ninth All India Conference of the Society for the Study of Industrial Medicine in Madras in February Dr. U. K. Rao said that medicine should consider the complex problems that link the health and welfare of the workers and their families. He suggested that industrial medicine should form part of the training of every physician. Accidents in factories are costly to industry both on the production front and on the efficiency front. Safety-first programs should therefore receive a high priority. The balance between mechanization and employment must be carefully managed in order to avoid creating fear, mistrust, and anxiety among the workers. He also suggested the establishment of institutes of occupational health to provide the requisite training to specialists in industrial medicine. Referring to the Employees' State Insurance Scheme, he said that from the point of view of the worker, it was distinctly a step forward. There have been many obstacles to the smooth working of this scheme but they are being gradually eliminated.

Venographic Studies of Chronic Filariasis.—U. S. Arora and co-workers (*Bulletin of Calcutta School of Tropical Medicine*, vol. 5, October, 1957) made venographic studies of the veins in the extremities of 15 patients with chronic filarial lymphedema. The lymphedema was unilateral in all patients so the opposite limb could be used as a control. The duration of illness varied from two to five years. The edema was solid nonpitting or slightly pitting. No microfilariae could be found in any of the affected limbs. In the leg the long and short saphenous veins were within normal limits in 11 of 12 patients, there being no dilatation stenosis or local intramural or extramural obstruction. The deep leg veins also

appeared normal. In the thigh the long saphenous and femoral veins showed no abnormality. The veins in the lymphedematous upper extremities were also normal. Thus there was no indication of any anatomic or functional disturbance in venous systems of the affected limbs to account for the edema.

Hemophilia.—J. B. Chatterjee and co-workers (*Bulletin of Calcutta School of Tropical Medicine*, vol. 5, October, 1957) stated that hemophilia is a syndrome consisting of deficiency of antihemophilic globulin (AHG), plasma thromboplastin component (PTC), and plasma thromboplastin antecedent (PTA). AHG and PTC are indispensable for normal coagulation. Deficiency of AHG and PTC ordinarily occurs only in males while PTA deficiency may occur in both sexes. The authors attempted to ascertain the specific deficiency factor in 14 patients with hemophilia. In addition to platelet counts and a study of platelet morphology, they determined the bleeding and coagulation time, capillary resistance, clot retraction time, and levels of prothrombin plasma labile factor, serum prothrombin conversion accelerator, and fibrinogen. All the tests were normal except the coagulation time which was prolonged in all but two patients, the serum prothrombin activity which was high, and the prothrombin consumption which was low in all patients. Results of the corrective studies showed deficiency of AHG in nine patients, of PTC in three, and of PTA in one, a 56-year-old woman who had hematuria. One patient had a combined deficiency of AHG and PTC. The ratio of the incidence of various deficiencies approximated that reported in other countries.

Diaminodiphenyl Sulfone.—Chatterjee and Poddar (*Bulletin Calcutta School of Tropical Medicine*, vol. 5, October, 1957) studied the uptake of diaminodiphenyl sulfone by patients with leprosy to determine the localization of the drug in the affected tissues. Biopsy specimens of healthy and affected tissues were made after a single oral dose of 4 μc per kilogram of body weight of the sulfone tagged with S^{35} was given to the patients. Autoradiographs of healthy and affected tissues showed a greater concentration of radioactive drug in the affected than in the healthy tissues. The localization in the affected skin was most marked around hair follicles, sweat glands, blood vessels, nerves, and areas of lymphocytic infiltration. The histiocytes, epithelioid cells, and foam cells also showed a high concentration.

Capillary Permeability in Chronic Filariasis.—Arora and Bhaduri (*Bulletin of Calcutta School of Tropical Medicine*, vol. 5, October, 1957) stated that the protein concentration of the peripheral lymph and the accumulated tissue fluid in chronic filarial lymphedema of the extremities is much higher than normal. To determine whether this is due partly to the presence of excessive leakage from the capillaries, the authors used the cuff experiment devised by McCance and Thrussel on 10 patients with lymphedema of forearm and hand on one side. The duration of the illness was between 20 and 50 years. An increased filtration rate was seen in all but one patient. Thus an increased capillary permeability together with the pathological changes in the lymphatics would appear to cause chronic filarial lymphedema.

NEW ZEALAND

Carbon Monoxide Hemoglobin Estimation.—J. Brueckner and F. B. Desmond (*Clin. Chim. Acta* **3**:173, 1958) described a simple and reliable spectrochemical method for the rapid estimation of carbon monoxide hemoglobin (HbCO). The quotient value of specific extinction coefficients of a hemoglobin pigment in solution measured at two wavelengths is a constant and characteristic figure. If two pigments are present in the same solution the quotient can be used to calculate the proportions of each pigment. The authors have further introduced the use of the ratio of extinction values at two suitable isobestic points of oxyhemoglobin (HbO_2) and HbCO to indicate the presence of other pigments or sources of interference which could adversely influence or offset the sensitive spectrophotometric measurements. In the methods hitherto described, though they are theoretically sound, little endeavor has been made to guard against such intereferences. The present method requires only 0.1 ml. of blood obtained by finger prick; 2 ml. of saponin-ammonium hydroxide diluting solution is added to the sample in a centrifuge tube. To obviate any possibility of dissociation of HbCO, mixing is done gently. The solution is then centrifuged for 10 minutes at 3,000 rpm. By strong transmitted light the fine clot which forms is easily seen and readily removed with a capillary pipette. The now clear solution is transferred to a 0.1-cm. cuvette, the extinctions (E) at 541, 561, 573, 577, and 597 mμ are measured and the ratios E_{541}:E_{561}, E_{577}:E_{561}, and E_{573}:E_{597} are calculated. The percentage of HbCO can be read directly from a standard graph.

Experimental Lung Transplantation.—Realizing that the biological barrier of tissue resistance will not allow successful homotransplantation of lung, except possibly in identical twins, J. Borrie and J. Z. Montgomery (*Proc. Univ. Otago M. School* **36**:1, 1958) reported that it seemed reasonable, however, to evolve a technique for completely excising and reimplanting a lung in the same animal and checking function by oxygen uptake studies before and after operation. A method for dividing and resuturing in turn the pulmonary artery, vein, and bronchus was

first devised, then complete excision and reimplantation were performed at the one operation. The left lung has been removed and reimplanted in 10 sheep. Because its upper lobe bronchus arises directly from the trachea, the right lung was not used. None of the 10 sheep survived beyond six days, early deaths being due to tension pneumothorax in one, operative hemorrhage in one, and bronchial obstruction in three and late deaths being due to a slowly developing thrombosis within the pulmonary artery or veins producing pulmonary infarction. Of five animals who had immediate postoperative differential bronchospirometry, however, two had ventilatory and oxygen-absorbing function similar to their preoperative tracings and one had a latent function made obvious when the right lung was occluded. These tracings indicate the pattern of respiration one may expect when successful lung homografting becomes a reality.

Hypnosis of Prisoners.—Dr. H. M. Buchanam reported at the annual conference of Justice Department psychologists that he used hypnosis for 16 difficult prisoners and that it was a better method of helping muddled and hysterical prisoners than the use of tranquilizing drugs, although the use of tranquilizers has not been given up. One subject was a young man with hysterical paralysis of the leg. Physiotherapy gave no relief, but hypnosis helped him to walk without crutches and to make a complete recovery. Another subject, a 22-year-old girl, was aggressive and insolent and required tranquilizers in large doses. After hypnosis the dose of the drug was reduced and finally cut out. The girl was released and entered nurse's training.

Bovine Tuberculosis.—At the Annual Conference of the New Zealand Veterinary Association, Dr. C. H. King reported that bovine tuberculosis was probably responsible for 40 to 50 new cases of tuberculosis in human beings and five or six deaths each year. The disease is a rural problem, and it seldom appears in the bovine form in townspeople. A highly dangerous practice is the feeding of rural children with unpasteurized milk, as some people still wrongly believe that milk containing the living bacillus of bovine tuberculosis confers immunity against the disease to the child. The general incidence of bovine tuberculosis in cattle in New Zealand is about 11%, but in vast areas it is 2% or less. In certain localities it reaches 50%. For any national scheme of eradication to be successful, it must initially operate on a voluntary basis, and restrictive controls should therefore be kept to a minimum. It is not yet clear how best to protect a tubercle-free herd from reinfection. The greatest problem to a national scheme of eradication is the shortage of trained personnel to undertake all the testing required.

SWEDEN

Urogenital Tuberculosis.—A. Beskow (*Nord. med.*, Feb. 20, 1958) sought for urogenital tuberculosis in such of the 367 patients admitted to Romanäs Sanatorium during the period 1950 to 1952 as had disturbances of micturition and albuminuria. In the three years, 1953 to 1955, the search for urogenital tuberculosis was made routinely in practically every case. In the first three years only 79 patients were examined for urogenital tuberculosis, which was found in 5. In the second three-year period 485 patients were thus examined, and urogenital tuberculosis was found in 9. Among this total of 14 patients there were 2 in whom both the guinea pig test and the culture were positive, and 12 in whom the guinea pig test was positive and the culture negative. There were three others in whom both tests were negative in the face of convincing evidence to the contrary. In two of these chemotherapy was responsible for the tests being negative. Comparing the merits of the two systems of examination, the selective and the routine, Beskow concluded that the former was reliable enough and much more economical.

Tropical Diseases.—Since March, 1955, facilities have been provided at the Jönköping fever hospital for the treatment of patients with tropical diseases hitherto scattered throughout Sweden. Dr. O. Gabinus (*Nord. med.*, March 27, 1958) reported 156 patients coming from the tropics have been examined for some tropical disease. Of these 24 were admitted to the hospital. Most of the 16 cases of malaria were diagnosed without microscopic evidence during a parasite-free interval, by means of an enlarged spleen, anemia, and recovery from various symptoms under treatment with chloroquine and primaquine. Infestation with the tissue nematodes was found in 41 patients including 19 with filariasis and 20 with acanthocheilonemiasis. The diagnostic complexity of the task was increased by the possibility of more than one nematode infestation in the same patient. Such duplication was observed in seven patients, and there was one with a triple infestation.

Hitler and Parkinsonism.—Professor K. A. Ekbom (*Svenska läk.-sallsk. förhandl.*, March 28, 1958) reported that it was not till 1945 that Hitler was said in public to be suffering from paralysis agitans. What was, perhaps, the clearest account appeared in 1951 when Guderian published his reminiscences of Hitler from whose presence he was banished for 14 months. At the end of this interval he was struck by the complete change in Hitler's appearance. His left hand trembled, he stooped, and his expression was stony. These changes were progressive, and after the attempt on his life in July, 1944, the trembling extended from his hand to the whole of

his left side. To mask this he used to cover his left hand with his right. His gait was dragging, his movements were slow, and his attendants had to slip a chair under him when he was about to sit down.

Pulmonary Tuberculosis of Old Age.—At the chest hospital to which he is attached, Dr. T. Bruce (*Quart. J. Swedish Nat. Tuberculosis A.*) noted that 20 years ago only 5% of the patients were over 50 years old. At present barely 25% of the recently admitted patients are under 35, while more than 33% are over 50. Before it can be argued that tuberculosis has become more frequent than it was in the elderly, account must be taken of the increased expectation of life and the greater proportion of old persons in the population. Källqvist has shown that in the last 15 years there has been practically no change in the frequency of pulmonary tuberculosis among persons over 50 but the declining incidence of pulmonary tuberculosis among the young, thanks to BCG vaccination, should ultimately improve the outlook for older persons.

UNITED KINGDOM

Bronchitis in Britain and Denmark.—In England and Wales bronchitis causes 25,000 deaths a year, accounting for 50% of the deaths due to respiratory disease and 5% of those due to all causes. These figures are much higher than those of other European countries and the United States. Christensen and Wood compared the mortality due to bronchitis in England and Wales with that in Denmark and investigated some of the possible factors responsible for the high prevalence of the disease in the former country. The mortality from bronchitis in England and Wales is 15 times that in Denmark. The excess mortality in England and Wales occurs at all ages for both sexes, although male mortality is much greater than female. In England and Wales the mortality from bronchitis is much greater in the towns than in rural districts, in contrast to the situation in Denmark where there is little difference in the two regions. A possible explanation of the greater mortality from bronchitis in England and Wales is its greater urbanization with accompanying atmospheric pollution. Another factor may be the difference in the national smoking habits of the two countries, the cigarette consumption of England and Wales being twice that of Denmark.

Reduction of the Side-effects of Morphine.—Shaw and co-workers (*Brit. M. J.* **1**:675, 1958) used cyclizine hydrochloride, an antihistaminic and amiphenazole, an analeptic used in the treatment of barbiturate poisoning, to control the side-effects of morphine. The use of cyclizine was suggested by Professor Shaw's earlier work indicating that some of the side-effects of morphine might be due to histamine release. Amiphenazole was used to counteract the mental depression caused by morphine. The initial tests were made on 46 volunteers, who were given 30 mg. of morphine. The main side-effects produced by this dose were dizziness, nausea, ataxia, mental depression, and tremor, which occurred in all the volunteers. In addition vomiting was noted in 62%, itching in 75%, and difficulty in micturition in 75%. All volunteers found it necessary to lie down on account of the side-effects. Forty subjects were then given 30 mg. of morphine parenterally and 50 mg. of cyclizine hydrochloride by mouth. This reduced the incidence of nausea from 100 to 42% and of vomiting from 62 to 25%. There was also some reduction in the incidence of dizziness, tremor, and difficulty of micturition. Only 40% of the volunteers found it necessary to lie down on account of side-effects in contrast to 100% given morphine alone. Amiphenazole in a dose of 40 mg. reduced the incidence of central-nervous-system depression from 100 to 45% and to a slight extent some of the other side-effects, although not as much as the cyclizine. The tests were repeated on 28 students, in whom morphine-induced vomiting was reduced from 57 to 11% by the use of cyclizine and amiphenazole. The authors have given up to 200 mg. of morphine for the control of chronic severe pain in 400 patients, covering the side-effects with 50 mg. of cyclizine and 40 to 100 mg. amiphenazole.

The Stiff-Man Syndrome.—The stiff-man syndrome, described by Ascher and co-workers (*Brit. M. J.* **1**:265, 1958), consists of a relentlessly progressive stiffness of muscles in the limbs and trunk, interspersed with painful spasms in the affected groups, which may be severe. The syndrome does not resemble any known disease, although the attacks resemble and are as severe as the muscle spasms of tetanus. No treatment has been found to arrest the disease or to relieve the pain. Each attack starts suddenly at any time, the calves of the legs being the parts mainly affected, although other muscle groups, such as those in the thighs, buttocks, back, chest, hands, and arms may be affected. There is often associated retention of urine. The muscles become rigid with the consistency of iron and show a coarse fibrillation. The attacks, which are described as agonizing, may last a few hours or several days. Apart from the spasms the general health my be good. Examination of two subjects with the syndrome revealed no abnormality except inability to elicit some reflexes owing to the muscle stiffness. The muscles appear normal in sleep and under anesthesia. Treatment with mephenesin, quinine, and chlorpromazine proved useless, and large doses of meperidine and morphine did not relieve the pain completely. Electromyography showed a normal pattern of discharge, and muscle biopsy re-

vealed nothing abnormal. The only abnormality found was a disturbance in phosphorus metabolism. A glucose tolerance test was followed by a rise instead of the expected fall in the serum inorganic phosphate level.

Alternative to Tranquilizers.—There is reason to believe that tranquilizers are being used too often and indiscriminately. Rathod described the treatment of two wards of chronic refractory mental patients by tranquility achieved by drugs and by improvement of the patients' environment. The two wards contained chronically disturbed psychotic women, mainly schizophrenic, ranging in age from 20 to 80 years. About 90% of them had been hospitalized for their mental condition for three or more years, during which time chlorpromazine or mepazine had been given. Without the knowledge of the patients or nurses the drugs were replaced by placebo tablets of indentical appearance, and at the same time intensive and varied occupational activities were introduced, such as teasing wool, needlework, knitting, games, physical training, musical evenings, and the formation of occupational therapy groups. Patients were also encouraged to take part in other recreational activities and to work in the departments of the hospital. Better and closer staff-patient relationships were fostered so as to create a friendly atmosphere. Data were collected from the nurses' reports, and the behavior of the patients under the tranquilizing regimen and occupational activity was compared. The results showed that changing the patients' environment and giving them occupational interests produced results just as good as those initially obtained with tranquilizers. The initial improvement resulting from the giving of chlorpromazine and mepazine was not maintained. Improvement occurred while placebos were being given, suggesting that they have some therapeutic value. Their withdrawal led to deterioration. Rathod concluded that giving the mental patient some interest in life produces results just as good as those obtained by the administration of tranquilizers. The use of the latter exposes the patients to possible toxic effects and the hospital to unnecessary expense.

Mass Radiography.—Mass radiography of the general public for the discovery of new cases of tuberculosis has been criticized on economic grounds. McDowell (*Lancet* **1**:632, 1958) showed that if used selectively it is of great value in picking up new cases. He agreed that random examination of all and sundry was wasteful. In the Birmingham region mass-radiography case-finding activities fell into two main categories. First, and most rewarding, were group-radiography sessions for the examination of groups likely to show a high prevalence, such as patients referred by general practitioners on suspicion, contacts with active cases, tuberculin-positive children, and teachers. Second, there were mass surveys of factory employees, older schoolchildren, and the general public, where the purpose was to radiograph large numbers of persons as expeditiously as possible to filter off those with symptomless active tuberculosis.

In addition to case finding, protective surveys were also made, the intention being to protect either a group or the individual rather than to find a high incidence of tuberculosis. These surveys included such groups as young recruits to armed forces, antenatal patients, students, and persons working with children. Mobile units were used for much of this work. The combination of group and mass radiography picked up 1,220 active cases in one year, the largest number of cases in any region. Half the active cases were infectious. The early minimal lesion of routine mass radiography is replaced in group radiography by a more extensive and sometimes cavitating condition. One more source of infection in the community is thus found and removed. The search for contacts has not the same urgency as the discovery of the minimal lesion. McDowell recommended that a mass radiography unit should consist of a static 100-mm. unit for group radiography and a lightweight mobile unit for mass surveys of selected high-prevalence groups. The static unit should be in the main hospital for the industrial area, where it can be used according to local demand. At other times it could be used for routine radiography of outpatients and for follow-up examinations. In 1956, 30% of all the reports of cases of respiratory tuberculosis in the Birmingham region came from the mass radiography service.

Infective Polyneuritis.—A. M. G. Campbell (*Proc. Roy. Soc. Med.* **51**:157, 1958) believes that the virus of feline enteritis may be the causative organism of infective polyneuritis. He treated six patients in whom the onset of the disease was directly related to an illness of the patient's cat, and he has heard of five other such cases. Typical of these cases was that in which a woman developed infective polyneuritis about a month after her kitten had what was probably feline enteritis. She herself attributed the illness to contact with the kitten, which she had nursed throughout its illness. A farm laborer who developed infective polyneuritis sent his cat to a woman 40 miles away to be cared for while he was ill. A month later the cat sickened and died of feline enteritis and the woman aged 65 was admitted to hospital with infective polyneuritis, from which she died 10 days later. There appears to be strong circumstantial evidence that this syndrome is at least occasionally linked with an illness of cats. Feline enteritis is a viral disease which is highly infectious among cats, chiefly affecting young cats and kittens. Probably 70% of all cats are infected at some time. Complement fixation reactions have

been carried out on the serum of patients with infective polyneuritis, using as antigen spleen and lung tissue from cats infected with feline enteritis virus. The results suggest that there is a distinct difference between the patients' blood and the blood of controls.

A Distinguished Octogenarian.—To commemorate the 80th birthday of Sir Gordon Gordon-Taylor, on March 18, the *British Journal of Surgery* issued a special Gordon-Taylor birthday number. Sir Gordon continues to take an active interest in his profession. Among other honors he holds an honorary fellowship in the American, Australian, and Canadian Colleges of Surgery, and his honorary degrees include the LL.D of Toronto and Melbourne and the M.D. of Athens.

Pulmonary Moniliasis.—McKendrick and Medlock (*Lancet* 1:621, 1958) treated a 9-year-old girl, who had pulmonary moniliasis complicating a case of fulminating influenzal pneumonia and whose chances of recovery appeared remote, with sulfadiazine and hydrocortisone. Two days after admission to hospital a heavy growth of Candida albicans was obtained from her sputum; 500,000 units of nystatin were given every six hours by mouth for eight days, and 500,000 units were introduced every four hours by nebulizer into her oxygen tent for four days. The aerosol was made by mixing 500,000 units of nystatin with 15 ml. of distilled water and atomizing this at a flow rate of 6 liters a minute, which exhausted the solution in about an hour. The child ultimately recovered. The authors were much impressed by the speed with which C. albicans disappeared from the sputum under treatment with nystatin, and they believe that the inhalations were the decisive factor in this. The child later returned with evidence of bronchiectasis at the base of her left lung, and Candida organisms were again recovered from her sputum. Her general condition, however, was excellent, and the view was expressed that the fact that Candida organisms were not completely eliminated in the acute stage does not alter the fact that the nystatin given by aerosol played an important part in her survival.

National Library of Medicine.—The medical section of the Library Association sent a memorandum to the Minister answerable to Parliament for the Department of Scientific and Industrial Research, which is planning a national lending library of science and technology. The association is gravely concerned because it is not intended to include medicine in the coverage of the new library. The memorandum referred to the service rendered by the National Library of Medicine at Washington, which is not only national but international, setting an example that has been the admiration of British medical librarians. The Royal Society of Medicine and the British Medical Association both have excellent libraries but lend books only to their members. Their stocks are insufficient in any case for interlibrary lending. The memorandum pointed out that it is not only the medically qualified that need a national medical library but also, and often to an even greater extent, those research workers with scientific qualifications working in allied fields. Access to medical literature is difficult for them. Medical institutions and research organizations cannot hope to cover all the books and journals necessary for research workers. If they are isolated from cities they cannot have extensive access to medical literature. Moreover the advances in medicine are recorded not only in journals but also in symposiums, research conference proceedings, and transcripts of tape recordings and by other means. These records cannot be provided by the individual working library, nor would it be economical for it to attempt to do so. Although each unit should have a working library there must be a central source of medical information. The needs of both medical and scientific workers might be met by providing a national library of medicine. This would be a supplement to, not a substitute for, local resources and would be best based on the existing collections of the Royal Society of Medicine. The new medical library could cooperate with the proposed National Lending Library of Science and make its services available on the same lines. If such a plan is not possible, the proposed National Lending Library of Science and Technology should consider covering in its science section the whole field of medicine in its broader aspects.

Suicide After Watching Television.—At an inquest at Havant, on a woman of 38 found with her head in a gas oven, her husband said that a television series entitled "Your Life in Their Hands" had profoundly affected her. Details of operations were shown and discussions held on cancer and its treatment. The woman's husband said that she feared she had cancer. At autopsy no evidence of cancer or of any other disease was found. The woman had previously worried about her eyes and had threatened suicide. The coroner returned a verdict of death from poisoning by carbon monoxide, which was self-administered while the woman's mental balance was disturbed. This was the second case of suicide attributed to mentally unstable persons viewing the B. B. C. telecast entitled "Your Life in Their Hands."

Physicians Build Hospital.—The New Victoria Hospital, New Malden, Surrey, is the first voluntary hospital to be built since before World War II. It is also the first hospital independent of the state medical service to be opened since all the hospitals were nationalized 10 years ago. It would require a

fresh act of Parliament to nationalize the new hospital. It cost $85,000, has 20 beds, and is managed by the local general practitioners.

Increased Pay for Service Physicians.—Increased rates of pay and marriage allowances are announced for doctors in the armed forces. This increase is timely as the rates of pay have always lagged behind those of physicians in civil practice and in the hospitals aided by the state. Even now a medical officer with the rank of lieutenant general earns about $3,500 a year less than a top hospital specialist. The new rates of pay apply only to regulars who have contracted to remain in the service for several years and who are based in the United Kingdom. The new annual rate of pay for an entrant, with the rank of acting surgeon-lieutenant (navy), lieutenant (army), or flying officer (air force) is $1,850, which is increased on marriage to $3,000. The pay of a surgeon commander, lieutenant-colonel, or wing commander, becomes $4,665, increased on marriage to $6,100. The highest pay is that of a surgeon vice-admiral, lieutenant-general, or air marshal, who receives $10,525, with a marriage allowance of $1,870. In addition all officers receive rations in kind or an allowance in lieu, amounting to $200 to $610. Education allowances have also been increased.

Blood Tests not Enforceable.—In a paternity case in Edinburgh an attempt was made to persuade the court to order a mother to submit herself and her daughter to a blood test. The case was one in which a corporal was seeking a divorce on the grounds of his wife's adultery. The court refused to make the order and dismissed the husband's appeal for lack of evidence. It was argued that the court, if it enforced the order, would be responsible for the compulsory infliction of a surgical operation, albeit a minor one, and this would be in law an assault on the person. The position with respect to the daughter was that as an infant she could not consent to an operation. As she was not even a party to the suit, it was impossible to compel her to submit to an operation to provide evidence. Without a test on the child, any test on the mother would be valueless.

Postoperative Metabolic Changes.—It is generally taught that after operations there are certain inevitable metabolic changes, such as negative nitrogen, potassium, and sodium balances. Abbot and co-workers (*Lancet* 1:704, 1958) presented evidence that operative trauma and anesthesia per se are only minor factors in determining the pattern of metabolic response to injury. They stated that the major factors are the dietary regimens, the complications, the previous nutritional state, and the sex of the patient. They believe that the impression gained by other workers that the postoperative metabolic disturbances are inevitable was due to the effects of an insufficient supply of calories, nitrogen, and electrolytes. By administering intravenously a solution containing 5% protein hydrolysate in 10% fructose solution and sufficient sodium and potassium salts to provide 75 to 125 mEq. each of sodium and potassium, the authors found that postoperatively patients need not lose excessive amounts of nitrogen, sodium, and potassium or lose weight. If there is extensive blood loss and if necrotic tissue or serious infection are present, large losses of these components occur. Although infection, hemorrhage, and tissue damage greatly increase caloric needs and accelerate metabolic processes, these effects can be minimized by an adequate intake of calories, protein, and electrolytes. At the same time, infection must be controlled, necrotic tissue removed, and blood loss corrected, if the patient's weight and the nitrogen and electrolyte balances are to be maintained.

Cost of Unnecessary Absenteeism.—Dr. H. W. Ashworth, a general practitioner in Manchester, investigated the extent of unnecessary absence from work by patients in his practice, a total of 3,300. Over a period of a year, during which the average number of items of service per year given to each patient was 4, he estimated that there were 10 for malingerers. These were refused certificates exempting them from their work and entitling them to sick pay. Sickness certificates were, however, issued to 44 women and 54 men, who extended their absenteeism beyond the time considered necessary on medical grounds. The women made 53 unjust claims and lost 634 days' work unnecessarily, for which they drew sick benefit. The men made 61 unjust claims and lost 640 days' work. Most of the women were married. In the same period 114 women and 209 men claimed sick benefit honestly. They lost 3,143 and 6,561 days' work respectively. There were also a group of 15 women and 17 men belonging to the chronic sick, accounting for 4,368 and 5,544 days respectively away from work. Dr. Ashworth estimated that 20% of those who claimed sickness benefit made a claim that was unnecessary or unduly prolonged. Of 21,754 days lost through sickness, 1,274 were lost unnecessarily. Social and domestic conditions sometimes provided extenuating circumstances, although the medical grounds were insufficient. This accounted for the absenteeism of 14 women and 11 men. It is calculated that 5% of the money paid out in sick benefit is unjustly drawn. In this group of 3,300 patients there is a hard core of 15 women and 17 men who unjustly draw about $10,415 a year in sick pay between them. Throughout the country a total of 2,352 billion dollars would be paid out annually in sick benefit on the basis of these figures of which 70 million dollars would be claimed unjustly.

CORRESPONDENCE

ESTROGENS TO INHIBIT GROWTH

To the Editor:—In view of the possible encouragement to practitioners to administer estrogens to tall peripubescent girls, there are some pertinent points in the interesting article of Dr. S. Charles Freed in THE JOURNAL, March 15, 1958, page 1322, wherein he describes the results of such therapy on two patients.

First, Dr. Freed does not state (*a*) the possible measurement errors of incremental growth in height. In measuring increments in six-month periods where one is dealing with such gains as 4.0 cm. to 0.32 cm., for instance, measurement error can be a very vital factor. He does not state (*b*) how he predicted the amount the patient would grow in height before maturity. Bayley and Pinneau (*J. Pediat.* **40**:423-441 [April] 1952) have shown the potential errors in such prediction before the age of 12 years and have suggested that supplementary tables are needed for children advanced or retarded in development. Accuracy of skeletal age assessment is clearly vital. Dr. Freed does not state (*c*) how he assessed the "normality of bone age." It is assumed that this means a bone age of the chronological age of the child and that the Greulich & Pyle atlas was used. Unfortunately in the peripubertal period, especially in the female where the total puberty period is so concentrated, this method of assessing skeletal maturity status when a fine measure is needed is sometimes not truly adequate for this purpose. He does not state (*d*) in what stages of puberty were both the patients and through what phases of this period they passed during observation. Most workers agree that there are five arbitrary stages, and these are of great help in assessing the progress in such cases (Reynolds and Wines, *Am. J. Dis. Child.* **75**:329-350 [March]; Tanner, Growth at Adolescence, Springfield, Ill., Charles C Thomas, 1955).

Second, the crux is, at what stage of the puberty stature spurt were the patients when therapy was started? It is a well-established and accepted fact that menarche occurs almost invariably after the apex of the height spurt has passed (Tanner, 1955). A table constructed from Doctor Freed's data, standardizing incremental periods at six months, and interpolating from his stated velocity data at the beginning of therapy shows certain patterns.

On the evidence given, either of these patients could, in fact, have passed the time of the apex of their height spurt, and the data could just as well indicate two girls who were somewhat constitutionally tall, who had reached their maximum height gain early and were on the descent, and who physically matured at an earlier than average age.

Third, it is interesting that the incremental curves in both cases are bizarre and show a sharp decline after the initial assessment of velocity (and this certainly coincided with the start of therapy), but then in the second six months the curves rise again (still during therapy) before falling off to zero. This may be explained by errors of measurement or by an initial effect of the therapy to diminish height gain and then by a lessening of the effect. Doctor Freed has also postulated that (*a*) chondroplasia (as measured by height gain) is

Data on Dr. Freed's Two Patients

	Case 1		Case 2	
Patient's Age, Yr.	Height Achieved Cm.	6-Monthly Increments, Cm.	Height Achieved, Cm.	6-Monthly Increments, Cm.
11	...	...	165.5	...
11½	160.0	...	169.0	3.5
12	163.0	3.0	170.0	1.0
12½	164.0	1.0	171.0	1.5
13	...	2.0	173.0	2.0
13½	168.0	2.0	173.0	0.0
14	168.32	0.32	174.0	0.7
14½	168.32	0.0	...	...

inhibited by estrogens and (*b*) osteogenesis (as measured by "bone age" assessment) is greatly accelerated.

Before this can truly be evaluated it will be necessary (*a*) to match a reasonable number of treated and untreated tall prepubescent girls; (*b*) to assess skeletal maturity status by as fine a measure as possible (Tanner, *Proc. Centre Int. de l'Enfance Conf. on Growth Studies*, Brussels, 1958) and, in any case, concomitantly with regular height measurements; and (*c*) to record, also concomitantly, the stages of puberty through which the patients are passing. On the evidence so far it might be wise to carry the study of the place of estrogen therapy in such cases a little further before recommending it to physicians.

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LAW DEPARTMENT

MEDICOLEGAL ABSTRACTS

Malpractice: Translumbar Aortography; Res Ipsa Loquitur.—This was an action for damages resulting from the alleged negligent performance of a translumbar aortogram. From a verdict and judgment in favor of the plaintiff, the defendants appealed to the district court of appeal, first district, division 1, California.

The plaintiff was 55 years of age with a history of eye condition indicating premature aging. He was referred to Dr. Gerbode, one of the defendants, by his family physician. His chief complaint, when Dr. Gerbode examined him, was cramping pains in his legs, mostly in the calves, causing intermittent limping. This condition had started gradually, becoming increasingly more severe. He complained of pain in his hips and lower back on exercise. He also had abdominal pain on the right side. No pulses below the femoral pulse on each side were palpable. There was a weak femoral pulse on the left and none on the right. The legs blanched when they were raised. This is a characteristic of advanced arterioinsufficiency. Dr. Gerbode diagnosed a probable occlusion of the abdominal aorta, which had impaired the blood supply to the legs and other areas, and an advanced arteriosclerosis. He advised the plaintiff that he had evidence of serious circulatory disturbance, that the examination indicated that plaintiff might have a block in his abdominal aorta, and that there was something else wrong, as shown by the pain in his right side and back. Dr. Gerbode told the plaintiff of the seriousness of his condition and urged that the plaintiff enter the hospital for a thorough evaluation of his condition; that one of the things the doctor wished to have done was a study of the plaintiff's aorta, which would entail an anesthetic and an injection of some material into the aorta to localize the block; also x-rays of his gastrointestinal tract would be taken. Dr. Gerbode stated that if the clinical findings were borne out by the examination contemplated, his condition would be helped by an operation removing and replacing a segment of the aorta. Such an operation would improve the circulation to his legs and back and prolong his life.

The plaintiff entered the hospital, and Dr. Gerbode requested in writing that the aortography be performed by the hospital's x-ray department. The normal procedure in such cases is for the attending surgeon to tell members of the house staff team who are to perform the procedure basically what the problem is. Dr. Gerbode did this with Dr. Ellis and Dr. Andrews of the staff. Dr. Ellis was to perform the aortography. He had had five years' practice in surgery and was in charge of all special diagnostic procedures at the hospital, such as aortographies, that had to do with the injection of radio-opaque or contrast material in various arteries and blood vessels of the body.

Dr. Ellis called on the plaintiff in his hospital room and informed him that he was to do the aortography. He explained that he would inject some material into the aorta and take films at that time to see if they could ascertain the precise condition of plaintiff's circulatory system. On the afternoon of Jan. 8, Dr. Ellis went to the x-ray room, where the plaintiff was lying on a table. Present were the anesthesiologist, the radiologist, and several technicians. Dr. Gerbode was there at the beginning of the procedure but gave no instructions and did not participate in any way. The plaintiff was already anesthetized and asleep. Dr. Ellis was inserting the needle into the plaintiff's aorta when Dr. Gerbode came in the room. As the patient was apparently in good condition, Dr. Gerbode left and did not see the patient again until the next morning.

An aortography is a procedure requiring an anesthesiologist, a radiologist, and a surgeon. The function of the surgeon is to insert the needle necessary for the injection of material into the aorta and to discuss with the radiology department the materials used and the timing. A hollow No. 16 or No. 18 needle is used. The hollow is closed with a metal rod or stylette. It is approximately .03 in. in diameter and 6 in. long. The patient is placed on his abdomen, face down on the table, and given a general anesthetic. A sensitivity test is then done to determine if the patient is sensitive to the radio-opaque material to be used. The needle is inserted to the left of the spinal column approximately 3 to 4 in. to the left of the midline of the back underneath the 12th rib. The needle is inserted in an upward direction toward the front of the body so as to enter the aorta which lies in front of the spinal column. The material used in this case was a 70% solution of sodium acetrizoate (Urokon sodium). One cubic centimeter of it was injected into a vein in the plaintiff's arm, and he appeared not to be sensitive to it. After the surgeon feels the needle penetrate the wall of the aorta, a metal rod is removed from the needle and blood flows from the aorta through the hollow needle. A syringe is then attached to the needle. In this case 30 cc. of sodium acetrizoate were then injected at a fairly rapid rate. The defendant's witnesses testified that there was no difficulty in inserting the needle on the first attempt and that it was only inserted once. The injection took only a few seconds, and then a series of x-rays were immediately taken by a machine already in position. While the films were still wet Dr. Ellis

and the radiologist examined them. They showed that the descending aorta in the abdomen just below the vessels leading to the kidneys was blocked, and it seemed desirable to take additional x-rays in order to determine the extent or length of the block. During this time the plaintiff was kept under anesthesia and the needle remained in place, it being the custom so to do while the doctors are determining whether additional x-rays are necessary. This obviates the necessity of again inserting the needle. The doctors hoped that by changing the timing of the pictures in relation to the time of making the second injection they might be better able to delineate the vascular tree. Twenty cubic centimeters of sodium acetrizoate were then injected, without changing the position of the needle, and additional x-rays were taken, particularly of the body further down than in the first pictures. The entire procedure seemed to proceed in a normal manner, and the patient seemed that evening to have recovered from the anesthesia. The next morning when the plaintiff awoke his lower extremities were paralyzed.

The trial court had instructed the jury that the doctrine of res ipsa loquitur applied in this case, and the defendant's principal contention on appeal was that such instruction was error. The application of the doctrine in malpractice cases, said the court of appeal, is a development of comparatively recent years. Before that time, the facts that medicine is not an exact science, that the human body is not susceptible to precise understanding, that the care required of a medical man is the degree of learning and skill common in his profession or locality, and that even with the greatest of care untoward results do occur in surgical and medical procedures, were considered paramount in determining whether the medical man in a given circumstance had been negligent. But gradually the courts awoke to the so-called "conspiracy of silence." No matter how lacking in skill or how negligent the medical man might be, it was almost impossible to get other medical men to testify adversely to him in litigation based on his alleged negligence. This fact, plus the fact that usually the patient is by reason of anesthesia or lack of medical knowledge in no position to know what occurred that resulted in harm to him, forced the courts to attempt to equalize the situation by, in some cases, placing the burden on the doctor of explaining what occurred in order to overcome an inference of negligence.

The great difficulty in the application of the doctrine, continued the court, is in determining where to draw the line. To apply it in all cases where an unexpected result occurs would hamstring the development of medical science. No medical man would dare to use new procedures, especially in surgery, because if injury resulted he would be prima facie guilty of negligence. Medical science has developed in leaps and strides in the past few years. Procedures that 40 years or even 10 years ago would have been considered impracticable and fatal are now being successfully used; for example, surgery upon the heart. Even the procedure used in this case, translumbar aortography where the aorta is punctured and a foreign substance injected in order to determine the location of a suspected block, is one which but a few years ago would not have been attempted but one which is of great value in determining whether corrective surgery is needed and advisable. Thus a great responsibility rests upon the courts to determine the point at which the doctrine will apply in order to be fair to a patient who has received a result which according to common knowledge of either laymen or of medical men ordinarily would not occur without negligence and to be fair to medical men if there is a result which could occur without negligence and which should not impose upon them the presumption of negligence.

There can be little question, the court concluded, but that aortography and its results, because it is a relatively new diagnostic procedure, is not a matter of common knowledge among laymen. Very few laymen have ever heard of it. So far as laymen are concerned, it cannot be said that it is a matter of common knowledge that injury results only where there has been negligence in its use. Particularly is this so where it is performed upon a person with the advanced degree of arteriosclerosis possessed by plaintiff. It is a matter outside the realm of the layman's experience, and hence common knowledge as a basis for the application of the doctrine does not exist.

Was there any professional evidence calling for the application of the doctrine? There was no medical testimony upon which res ipsa loquitur could be based unless it was the testimony of the plaintiff's expert that the needle may have been inserted in the wrong place. There was no testimony that in aortography, without negligence, a needle could be inserted in a spinal artery. In fact, the testimony was just to the contrary, that there should be no great difficulty in inserting the needle in the aorta. There was, said the court, a conflict in the testimony, the defendant's experts testifying in effect that the sodium acetrizoate could have affected the spinal cord even if properly injected in the aorta and that such a situation might have occurred here; the plaintiff's expert testifying in effect that the x-rays showed the needle to have been inserted in the wrong place. The jury were not told that the doctrine could apply only in the event they found

that the needle had been inserted in the wrong place. On the contrary, the court instructed the jury that as a matter of law, from the "happening of all the events involved in this case, however, as established by the evidence" the inference of negligence arose. The jury were given no opportunity to determine the facts upon which the doctrine would or would not arise. This was prejudicial error.

The defendants also contended that the trial court had erred in holding the defendant Gerbode personally liable for any negligence there might have been in the performance of the aortography. Four doctors testified that it was not customary for the attending physician to perform, or to be present at the performance of, an aortography, and that it is customary to have such a procedure performed by the hospital personnel who are accustomed to working together in the performance of this and other complicated diagnostic procedures and perform them regularly. While Dr. Gerbode ordered the aortogram, and would be responsible for any negligence in prescribing such procedure, he cannot be held liable for the negligence of the team in the actual performance of it, as he neither participated in, nor had the right to direct it. When a patient is placed in a hospital his attending physician orders many procedures to be undertaken by the hospital staff or employees. The attending physician cannot be held liable for acts over which he had and could have no control. To hold that the attending surgeon who does not participate nor have the right to participate in the procedure is liable for the acts of a competent team supplied by the hospital would be against the best interests of patients generally. The patient, by the use of such team, gets the benefit of medical people who have become experts in the particular procedure. Other arguments attempting to hold the defendant Gerbode personally responsible were also overruled.

Another contention raised on appeal involved the legal effect of a manufacturer's brochure. The trial court gave an instruction to the effect that if a surgeon seeks fields of experimentation in treating his patients he is accountable for any damages proximately caused by any unskillful treatment of the patient. A further instruction was given to the effect that if sodium acetrizoate was injected in greater amount than that recommended by the manufacturer's brochure and if the jury found that such injection constituted experimentation, then all participating would be guilty of negligence unless the patient was first warned of the experimentation and consented to it. The first question to be considered, said the court, is the admissibility of the brochure. It was published by the manufacturer of the sodium acetrizoate. It stated that for translumbar aortography in an adult, "10 to 15 cc. of 70% Urokon is adequate" and that aortography should not be repeated within 24 hours. The plaintiff contended that this negatived a second injection. The defendants contended that it negatived only a second insertion of the needle. The uncontradicted evidence was that the second injection, if deemed necessary, is customary. In the "first run," in the plaintiff's case, 30 cc., and in the "second run" 20 cc., a total of 50 cc. were injected. There was no expert testimony that the amount used was improper. In fact there was testimony that as high as 50 cc. were customary on the first run. The court thought it was significant that the brochure recommended the use of 50 cc. of sodium acetrizoate in another procedure involving injection of the contrast medium for visualization of the heart itself.

The defendants and amicus curiae urge that a manufacturer's brochure is not admissible in evidence and does not establish a standard of care. They contend that a drug manufacturer's recommendations are always conservative and are quickly outdated, that the manufacturers expect, and the custom is, that after a material has been available for a period of time, physicians using it rely primarily on their own experience and the published literature of colleagues concerning its use in actual practice. They contend that the miraculous developments that have taken place in the effective use of antibiotics and other drugs might never have been accomplished if physicians were required to follow blindly the suggestions of the manufacturers who prepare but do not use them.

The court of appeal said that the brochure was admissible but that it cannot establish as a matter of law the standard of care required of a physician in the use of the drug. It may be considered by the jury along with the other evidence in the case to determine whether the particular physician met the standard of care required of him. The court also held that the mere fact of a departure from the manufacturer's recommendation, where such departure is customarily followed by physicians of good standing in the locality, does not make that departure an "experiment." There was in this case no evidence of experiment, and the instructions concerning "experiment" should not have been given.

Because of the ruling of the trial court on the question of res ipsa loquitur, and for other reasons, the verdict of the jury in favor of the plaintiff was reversed and the cause remanded for a new trial. *Salgo* v. *Leland Stanford Jr. University Board of Trustees, et al,* 317 P (2) 170 (Calif.) 1957.

MEDICAL LITERATURE ABSTRACTS

INTERNAL MEDICINE

Farmer's Lung—A Form of Pneumoconiosis Due to Organic Dusts. R. C. Frank. Am. J. Roentgenol. **79**:189-215 (Feb.) 1958 [Springfield, Ill.].

Farmer's lung, which has been described also under several other terms such as thresher's lung or harvester's lung, has received little attention in the American literature. The author presents observations on 27 patients with farmer's lung, some of whom have been followed up for 6 years to evaluate the presence of complications and permanent disability. Gradations in severity occurred. The syndrome developed after exposure to dusts in the handling of moldy hay or silage. Moldy grains were occasionally indicted, and even plain silage was not infrequently at fault. Symptoms in a few patients followed inhalation of the "steam" of silage, but this occurred weeks after ensiling on "opening" the silo and, therefore, would not likely be due to nitrous dioxide, the agent believed responsible for silo-filler's disease. Shredded corn stalks and dust from fresh hay and grain were also responsible for some cases. A minor form of the disease apparently occurs, involving dyspnea, chills and fever, and night sweats lasting a day or 2 after exposure to clouds of dust associated with threshing fresh grain. The symptoms pass quickly and are not followed by permanent disability. No cases of this minor form are included in this series. A typical acute episode is characterized by increasing dyspnea, cough which is usually nonproductive, fever and chills, night sweats, and weight loss.

The onset of the disease in the 27 patients reviewed followed 3 clinical patterns. The 11 patients of group 1 included the most spectacular ones, in that the acute attack followed a single exposure to unusual quantities of moldy hay, grain, or silage in the case of all but 1 patient. The exception was exposed to silage "steam" on opening the silo. In group 2 (9 cases), symptoms occurred after repeated exposure to moldy hay, grain, or silage over a period of time, usually a winter season. Patients of group 3 (7 cases) complained of symptoms after exposure to different inciting agents over a period of years. The severe acute exacerbation then occurred without any one particularly outstanding episode of exposure. These patients mostly had apparent sensitization to corn silage rather than to moldy hay. The author believes that 2 reactions are probably involved in the disease process. There is an initial pulmonary response to inhalation of organic dusts, involving a granulomatous reaction with associated interstitial fibrosis. Later sensitization to such dusts is believed to occur, and there is progressive pulmonary fibrosis on repeated exposures.

The dusts involved are most often those from moldy hay, grain, or silage, and the heavy fungal spore content of such dusts is believed largely responsible for the disease, although rarely the syndrome is due to vegetable dusts which are not very moldy. The pulmonary reaction to the fungal spores is due to their action as foreign bodies, and the disease is not believed to represent a pulmonary infection or mycosis. The causation and mode of progression of farmer's lung is still largely unknown, but present knowledge suggests that it is a form of pneumoconiosis due to organic dusts. A change of occupation should be recommended to patients with farmer's lung, and preventive measures should be advocated to save farmers from this disease. The author hopes that this report will stimulate further investigations into the many problems of this complex disease.

Trials of an Asian Influenza Vaccine: Fourth Progress Report to the Medical Research Council by Its Committee on Influenza and Other Respiratory Virus Vaccines. Brit. M. J. **1**:415-418 (Feb. 22) 1958 [London].

Four vaccines were made from the egg-adapted line of the Asian influenza strain A/Singapore/1/57; vaccine A contained 20,000 hemagglutinating units per dose, vaccine B contained 14,000 units per dose, vaccine C contained 7,000 units per dose, and vaccine D contained 3,500 units per dose. The hemagglutinating units of virus were in each vaccine adsorbed onto 10 mg. of aluminum phosphate per dose, and the dose in each was 1 cc., inoculated deep subcutaneously into the upper arm. Two groups of 60 volunteers each, mostly young men in Army and Royal Air Force units, were divided into 4 subgroups, each to receive 1 of the 4 vaccines. Two serum samples were obtained from each vol-

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unteer, the first just before inoculation and the second 3 weeks later. The antibody response to a single dose was low with each strength, although there was a somewhat greater response to the strongest. A second dose given 3 to 4 weeks later gave much greater antibody response.

The relative values of 2 doses, each of about 7,000 hemagglutinating units, 1 dose of about 7,000 hemagglutinating units, and 1 dose of 20,000 hemagglutinating units of the Asian influenza strain A vaccine were studied in field trials on volunteers, consisting of boys attending public schools, students at teachers' training colleges, and members of miscellaneous centers. The group of boys attending public schools were divided into 3 subgroups, 1 receiving 20,000 hemagglutinating units of the Asian influenza strain A vaccine, 1 receiving a polyvalent virus A vaccine, and 1 receiving a vaccine of the influenza B type. The groups of students at teachers' training colleges and the members of miscellaneous centers also were divided into 3 subgroups, 1 receiving 2 doses of 7,000 hemagglutinating units of the Asian influenza strain A vaccine, 1 receiving 1 such dose, and 1 receiving a vaccine of the influenza B type. A total of 3,093 persons were given 1 or the other of the 3 types of vaccine used. Severe epidemics of influenza took place in the public schools, and, subsequent to 8 days after the inoculation with 1 dose, a definite preventive effect was apparent in the group given Asian influenza strain A vaccine. After that interval of time the influenza attack rate fell to 33% of the attack rate observed in the other 2 subgroups given non-Asian influenza vaccine. The equality in the attack rate in these other 2 subgroups suggests that no protection against Asian influenza was conferred by the polyvalent virus A vaccine (although the young ages of the boys concerned may have been a factor in this). At a much lower epidemic level a similar protective effect of the Asian influenza strain A vaccine was observed in the groups of students at the teachers' training colleges and in the members of the miscellaneous centers.

Some Comments on Septicemia Due to Infection with Staphylococcus. P. Meriel and A. Fournie. Semaine hôp. Paris 34:392-399 (Feb. 12) 1958 (In French) [Paris].

The authors report on 5 men and 5 women, between the ages of 25 and 64 years, with septicemia due to infection with Staphylococcus pyogenes var. aureus, who were observed on a general medical ward of a hospital in Toulouse, France. Acute septicemia associated with endocarditis occurred in only 2 of these patients, 1 of whom died. The other 8 patients presented the subacute aspect of the disease with a local suppurative process as the principal feature; this may make the diagnosis difficult or may raise difficult problems concerning indications for surgical intervention. Metastatic abscess in the kidney, pyonephrosis, or a perinephric phlegmon occurred in 3 patients, and a focal nephritis in 6. Pyopneumothorax developed in 1 patient, an interhepatodiaphragmatic suppuration appeared in another, and the infection became localized in bones and joints in 2 patients. These observations suggest that there is still a relatively high incidence of septicemia due to infection with Staphylococcus organisms despite the increased therapeutic use of a large number of antibiotics with a broader action. The incidence of the subacute or chronic forms is on the increase and exceeds that of the acute and superacute forms. Blood cultures should, therefore, be practiced early and systematically in all patients with a febrile syndrome associated with chills and a sudden severe onset. This diagnostic method is simple, yields results rapidly (in general, within 24 hours), and is also of therapeutic value regarding the institution of treatment with antibiotics to which the pathogenic organisms are sensitive.

A Review of 182 Cases of Tetanus. R. Molphy. M. J. Australia 1:141-145 (Feb. 1) 1958 [Sydney].

The author reviewed the records of 182 patients with tetanus, who were treated at the General Hospital and at the Children's Hospital in Brisbane, with 2 objects in view: (1) to improve her own knowledge of the natural history of the disease and (2) to be able to recognize patients in whom curarization with intermittent positive-pressure respiration should be undertaken early. The 182 cases included some of each type of tetanus. There were 137 patients who had generalized spasms, and of these 76 (55%) died. The total mortality rate was 44%. There were 40 deaths among the 111 patients less than 20 years old (37%), whereas of the 8 patients over 70 years of age 6 died. Of all deaths, 83% occurred in the first week, and there were almost twice as many on the second day as on any other single day.

The average incubation period was somewhat longer in the patients who survived than in those who died. The period of onset proved to be the best guide to the severity of the disease. There were 137 patients with generalized spasms, and of these 83 (60%) had periods of onset of 48 hours or less. Of 35 patients who had periods of onset ranging from 4 to 24 hours, only 5 lived, and two-thirds of those who died did so in the first 3 days and as a direct result of uncontrolled spasms. Thirty-six patients had periods of onset ranging from 24 to 48 hours, and of these 12 lived; only one-third of the deaths resulted from uncontrolled spasms. In 79 patients spasms appeared after the second day or not at all; 20 of these patients died, none as a direct result of uncontrolled spasms. A significant pointer toward the advisability of institut-

ing complete neuromuscular blockade early is the high mortality associated with spasms in patients with a period of onset of 24 hours or less.

The author stresses the need of careful nursing and the extreme importance of postural drainage of pharyngeal secretions throughout the whole illness. She thinks that, except in mild cases, the intravenous route should be used as the mainstay in sedation to control spasms, as any other route gives too slow a control. Discussing the choice of drugs, she says that elixir mephenesin (Myanesin), chloral, and morphine can be used in mild cases and for convalescent patients. If the patient can swallow well, then the tablets of mephenesin may be used. Mephenesin given intravenously has a place in therapy in many cases of tetanus. It will rapidly control the severity of spasms; the frequency is not so much affected. It can be combined with a hypnotic and an analgesic; for example, it may be used with chloral given orally and morphine given subcutaneously, if the patient can swallow, or, if the patient has dysphagia, with phenobarbitone and pethidine given intramuscularly. Mephenesin can also be combined in an intravenous drip administration of 0.1% thiopentone solution and pethidine given intramuscularly. The danger of hemolysis or of respiratory depression with the use of mephenesin can be avoided by keeping the dosage low.

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Advances in Rabies Treatment: An Experimental Evaluation. N. Veeraraghavan, A. Balasubramanian and T. P. Subrahmanyan. Bull. World Health Organ. **17**:943-962 (No. 6) 1957 [Geneva].

Inquiries into various methods of treatment for rabies have been in progress at the Pasteur Institute of southern India during the past 3 years. In this paper a brief account is given of the important results of treatment with (1) antirabies serum alone, (2) 5% Semple vaccine, (3) a combination of serum and vaccine, and (4) high-egg-passage, chicken-embryo-adapted rabies vaccine with and without serum. Healthy guinea pigs, weighing about 400 Gm., were used in the protection experiments. Mice were employed for serum neutralization tests. The challenge virus was the lyophilized canine submaxillary gland suspension of a virus strain. With a short needle, 0.1 ml. of the selected dilution of the virus was inoculated into the right-sided gastrocnemius muscles of the guinea pigs.

When antirabies serum was given alone, either before or after infection, it definitely prolonged the incubation period, but it had no saving effect. Serum seemed to confer some protection when it was obtained from animals of the same species which had survived an infection with the particular challenge virus. With doses of 5% Semple vaccine, comparable to those administered to human beings, it was possible to confer protection on animals against virulent strains of street virus, provided that the treatment was started 7 days before challenge. Combined therapy with serum and vaccine given after infection was of great value under certain conditions. There appeared to be an optimum in the relationship between the quantity of serum given and the antigenicity and dosage of vaccine administered. High-egg-passage Flury vaccine given before infection gave good protection, but serum and high-egg-passage Flury vaccine administered after infection were not of value against an Indian strain of street virus.

Peptic Ulcer in Poorer Communities of West Bengal: Analysis of 100 Proved Cases. S. C. Chatterjee, D. C. Das and S. N. Sengupta. J. Indian M. A. **30**:35-42 (Jan. 16) 1958 (In English) [Calcutta].

The authors studied certain aspects of peptic ulceration in 100 patients who were admitted to a medical ward of a Calcutta hospital. Most of these patients were of the lower income groups. The series included 89 patients with duodenal ulcer, 8 with gastric ulcer, and 3 with concomitant ulcer. Thus, the ratio of duodenal to gastric ulcer was 11:1. There were 88 men and 12 women, representing a male to female ratio of 7.3:1. Duodenal ulcer was more common than gastric ulcer in both sexes, but while the ratio of duodenal to gastric ulcer was 16:1 in men, it was only 3:1 in women. The age of maximum incidence was in the third and fourth decades of life. A striking feature was that the Moslems had a relatively low incidence of peptic ulcer. In commenting on this fact, the authors point out that Moslems eat food cooked with onion and garlic, whereas Hindus do not. Garlic is a carminative and has actually been used in the treatment of peptic ulcer. It is possible that this herb has not only a curative but a prophylactic effect as well. Investigations on this question are being carried out. The symptoms of peptic ulcer varied widely, but complications, such as pyloric obstruction and hemorrhage, seemed to be rather frequent in these patients. Seventy-three per cent of the patients who had hyperchlorhydria had uncomplicated duodenal ulcer, but the authors are uncertain whether this has any definite significance. There was no relationship between gastric acidity and the chloride level of the blood.

Painful Nonsuppurative Swelling of Costochondral Cartilages (Tietze's Syndrome). E. H. Karon, R. W. P. Achor and J. M. Janes. Proc. Staff Meet. Mayo Clin. **33**:45-53 (Feb. 5) 1958 [Rochester, Minn.].

Observations are presented on 13 patients with Tietze's syndrome (benign, painful, nonsuppurative swelling of one or more of the costochondral cartilages) who were encountered at the Mayo

Clinic during 1955 and 1956. The most common presenting syndrome is pain in the anterior thoracic wall, although rarely swelling of a costosternal juncture may precede the onset of pain. The pain is usually localized to the site of the affected cartilage, but it often spreads and may involve the neck, shoulders, or arms. The onset may be gradual or abrupt, with wide variation in severity. Inclement weather, anxiety, fatigue, and recumbency may intensify the pain. It may be aggravated by coughing, sneezing, deep breathing, or activity, and it may simulate pleuritic pain. Duration of discomfort varies from a few days to several months. The presence of a firm bulbous or fusiform swelling of one or more of the costosternal cartilages is essential in making the diagnosis of Tietze's syndrome. Tenderness may not be noted initially and is frequently one of the first findings to disappear. The swelling rapidly reaches maximal size and then either remains stationary or slowly regresses. Spontaneous regression rarely occurs before several months have elapsed, but complete recovery is the rule.

A review of the literature revealed 159 cases of Tietze's syndrome (only 7 in the American literature), but the authors feel that the condition is probably more frequent than the literature indicates. The second costal cartilage is most frequently involved. Tietze's original suggestions concerning the causal role of tuberculosis and malnutrition have not been confirmed. A sprain involving the ligaments and capsule of the costosternal joints after trauma, such as that from coughing, might well produce the picture of Tietze's syndrome. This would fit well with the natural history of the syndrome, as most sprains require 5 to 6 weeks to heal. Synovitis could also be a causative mechanism, either as the accompaniment of a sprain or secondary to an inflammatory process, but none of these explanations fully accounts for the clinical or anatomic findings, and the exact cause is unknown. Tietze's syndrome must be differentiated from other causes of thoracic pain, especially those involving the thoracic wall. Concern regarding heart disease or cancer often brings the patient for medical attention and must be carefully evaluated. There is no specific treatment for this syndrome. Symptomatic treatment, consisting of reassurance, local heat or counterirritants, and analgesics, suffices in many cases. Surgical excision of the lesion has been advocated by some, but the authors do not feel that this is warranted. In 5 of their 13 patients prompt relief of pain, together with reduction of swelling, was obtained with local injection of 20 to 37.5 mg. of hydrocortisone. The authors feel that this form of treatment is advisable in patients with considerable pain or in whom the swelling is bothersome.

Renal Affections Caused by Abuse of Phenacetin. K. Larsen and C. E. Møller. Ugesk. læger **120**:114-124 (Jan. 23) 1958 (In Danish) [Copenhagen].

Attention is directed to the connection between large phenacetin consumption and renal disease. Clinical observations and investigations are reported which definitely testify to such a connection. Questioning of 698 patients, all over 20 years of age, who were admitted to the medical department of the Vejle District and Municipal Hospital during a 6-month period in 1957, revealed that 337 did not take medicines containing phenacetin, 156 reported occasional use, and 205 admitted daily consumption during at least a month. Twice as many women as men took phenacetin daily; the women also took larger doses and for a longer period of time. The renal function was reduced in 68 (33.2%) of the 205 patients who used phenacetin daily, in 17 (10.9%) of the 156 patients who used phenacetin periodically, and in 29 (8.6%) of the 337 patients who did not use phenacetin. The frequency of reduced renal function increased with the size of the dosage and the duration of use. Five cases are described. Examination of 17 patients whose total consumption over a period of years amounted to 7 kg. (15.4 lb.) or more showed a uniform picture of a renal lesion marked by reduced concentration ability and reduced filtration. The hypothesis is that the renal lesion depends on chronic hypoxia of the kidneys. The renal lesion caused by phenacetin and the acute tubulointerstital nephritis (lower nephron nephrosis) are regarded as the chronic and the acute form, respectively, of a disease due to oxygen deficiency in the kidneys. Employment of phenacetin in large doses often indicates genuine drug addiction and may lead to grave renal disease. The authors recommend that preparations containing phenacetin should be available only on prescription.

SURGERY

Patent Ductus Arteriosus with Pulmonary Hypertension. H. B. Shumacker Jr. and P. R. Lurie. A. M. A. Arch. Surg. **76**:179-192 (Feb.) 1958 [Chicago].

When patent ductus arteriosus is accompanied by pulmonary hypertension, diagnosis is more difficult, and surgical management is attended with special problems. In 1950 the authors abandoned the policy of treating patent ductus arteriosus by the multiple ligation-transfixion method and began to employ division and suture as the procedure of choice. The former method had yielded over-all good results but had not been free of disastrous consequences. With the method of division and suture, no fatality has been encountered in the treatment of uncomplicated patent ductus arteriosus

and no recanalization has occurred. The ductus was divided in 31 patients who had pulmonary hypertension. In 13 of these the hypertension was mild or moderate, and in this group the ductus was found to be large or fairly large. All the patients save 1 withstood operative treatment without difficulty. This 2½-year-old child was quite ill and was on bed rest and digitalis therapy prior to operation. The operation was uneventful, but because of persistent atelectasis, which did not respond to nasotracheal catheter aspiration, the patient was subjected to bronchoscopy 2 days after operation. Cardiac arrest occurred, and resuscitation could not be achieved.

The 18 patients who had marked pulmonary hypertension included some in whom the pulmonary pressure was equal to the systemic. In some with nearly systemic pressures the shunt was all, or practically all, from left to right. In others it was evident that considerable reversal was taking place. Bidirectional shunt was established in several cases. The murmur was atypical in 12 of the 18 patients. Considerable general cardiac enlargement was noted roentgenologically in most of them, and the right ventricle seemed to be enlarged in the majority. All the patients had cardiac symptoms. A number were in heart failure and were being treated with digitalis. Others had retardation of physical development. Death resulted in 2 of the 18 patients. Thus, there were 3 deaths in the 31 patients (10%) in whom patent ductus arteriosus and pulmonary hypertension were not associated with other congenital malformations of the heart.

Observations are presented also on 7 patients with patent ductus arteriosus and coarctation definitely or presumably associated with pulmonary hypertension, and on 16 patients in whom patent ductus arteriosus was associated with intracardiac and other anomalies. All the patients with coarctation and patent ductus arteriosus survived. The mortality was disastrously high in those patients in whom patent ductus arteriosus was associated with intracardiac and other anomalies. It is felt, however, that careful study of such cases will bring about improvement in results and may yield information of value in the management of other cardiac conditions. It is becoming increasingly obvious that surgical treatment of a variety of abnormalities, such as ventricular septal defect and the more complicated atrial septal defect, is hampered principally by associated pulmonary hypertension and pulmonary arteriolar sclerosis of severe degree. While the physiological mechanisms, at least early in life, may be quite different in these various disorders, pulmonary hypertension and pulmonary vascular sclerosis are common to them all. What is learned about the management of pulmonary hypertension in patent ductus arteriosus may be helpful in the solution of other problems. It would seem wise to study carefully before operation all patients with patent ductus arteriosus, in whom pulmonary hypertension is suspected, by cardiac catheterization and selective angiocardiography, preferably cineangiography. Efforts should be made to determine the direction and degree of the shunt. Pressure measurements and electrocardiographic tracings should be obtained, and a lung tissue specimen for biopsy should be secured at the time of operation.

Experience with Permanent By-Pass Grafts in Treatment of Occlusive Arterial Disease. R. A. Deterling Jr. A. M. A. Arch. Surg. **76**:247-260 (Feb.) 1958 [Chicago].

Because of discouraging clinical results in occlusive peripheral arterial disease with excisional therapy and end-to-end graft replacement, Deterling began in July, 1955, to employ bypass grafts in all patients operated on for acquired segmental occlusion of the major arteries of the lower extremities. More recently he extended their use to patients with occlusion of the thoracic and the abdominal aorta and with aneurysm of the thoracic aorta. He describes the surgical technique and then presents the results obtained with frozen homologous arterial grafts or with woven synthetic fabric grafts in 65 patients. The fact that the failure rate with the bypass homograft was only half that of excision and end-to-end graft in similar cases followed up for a comparable period of time is regarded as encouraging.

Clinical Use of Synthetic Arterial Substitutes in Three Hundred Seventeen Patients. E. S. Crawford, M. E. De Bakey and D. A. Cooley. A. M. A. Arch. Surg. **76**:261-270 (Feb.) 1958 [Chicago].

Arterial homografts have been generally accepted as the most satisfactory arterial substitute, but their disadvantages are unavailability and inconvenience of preparation. Efforts have been directed more and more toward development of a suitable synthetic replacement. This report is concerned with an analysis of a 3-year experience with tubes made of Ivalon (polyvinyl formalinized) sponge, Orlon taffeta, knitted nylon-Dacron, knitted Orlon, crimped woven nylon, and knitted Dacron used to replace or bypass aortic and peripheral arterial lesions in 317 patients. Functional results of all replacements used in the thoracic aorta of patients who survived operation were satisfactory. Immediate results in lesions involving the abdominal aorta and common iliac arteries were also good in all patients but 1, but late failures occurred in 5 patients. Early failure occurred in the 5 patients in whom Ivalon tubes were used to bypass peripheral occlusions. Circulation was restored in only 1 of the 2 patients in whom inflexible knitted Orlon tubes were used to bypass peripheral occlusions,

but it was restored in all 3 patients in whom peripheral aneurysms were replaced by the Edwards-Tapp tube and in 92 of 105 patients in whom occlusive lesions were bypassed. The recently designed flexible knitted Dacron tube was used successfully in 2 patients to bypass occlusive lesions in the femoral artery and in 1 patient to replace a popliteal aneurysm.

Although the functional results in this series of patients have been generally good, certain disadvantages still must be overcome in creating an ideal arterial replacement. The porosity of synthetic materials causes excessive blood loss, and the lack of accessory branches for replacing segments from which essential major branches originate has been a limiting factor in some cases. Tubes made of Orlon taffeta coated with vinyl plastic are difficult to insert and are not adaptable to problems requiring even minimal flexibility. Ivalon tubes, although more flexible, are still too rigid for general use and in this series produced a relatively high failure rate of 35%. Knitted Orlon and knitted nylon-Dacron tubes, when used to replace localized segments not requiring flexibility, restore and maintain circulation and, within the limitation of their semirigidity, are satisfactory substitutes. The Edwards-Tapp tube is both flexible and adaptable, although its ends fray and insertion is sometimes difficult. The recently devised knitted Dacron tube incorporates the desirable characteristics of all other available substitutes, and with the addition of accessory branches a complete range of adaptability may be obtained. Preliminary results of its application, experimentally and clinically, indicates that it is the best substitute yet developed. An addendum states that the knitted Dacron tube has been used as a vascular replacement in 237 cases and has proved to be the most satisfactory vascular replacement available.

An Evaluation of Stripping Versus Ligation for Varicose Veins. K. A. Lofgren, A. P. Ribisi and T. T. Myers. A. M. A. Arch. Surg. **76**:310-316 (Feb.) 1958 [Chicago].

At the Mayo Clinic, surgical treatment for varicose veins was direct dissection and partial extraluminal stripping from the beginning of this century to about 1927. Injection therapy alone then became the standard treatment during the next 10 years. In 1937 high ligation combined with retrograde injections became the accepted treatment. Complete stripping with a flexible intraluminal stripper having a larger acorn-shaped tip, which aided in telescoping of the vein, was started in 1947. The follow-up results from a group of 200 patients chosen at random for those who underwent high ligation and injection in 1940 were compared with those from a similar group of 200 patients who underwent complete stripping in 1950. The 1940 group was selected because in that year high ligation with retrograde injection was the treatment of choice. The 1950 group was selected because by that year complete stripping had become the accepted surgical treatment. Of 140 limbs examined 5 years or more after high ligation, 40% were classified as having excellent or good results, 5% fair results, and 55% poor results. Of 128 limbs examined 5 years or more after complete stripping, 94% were classified as having excellent or good results, 6% as having fair results, and none as having poor results. The incidence of recurrence requiring further surgical treatment was 36% for the limbs subjected to high ligation, whereas it was zero for the limbs subjected to complete stripping. Recanalization of injected superficial veins and the presence of persistent perforating veins were important factors in the high recurrence rate after high ligation. These results are convincing evidence of the superiority of complete stripping over high ligation in the surgical treatment of varicose veins.

Resection of Aneurysm of Thoracoabdominal Aorta: Involvement of Celiac and Superior Mesenteric Arteries, with Rupture into Psoas Muscle. E. S. Hurwitt, B. Seidenberg, S. C. Fell and D. S. Abelson. A. M. A. Arch. Surg. **76**:239-246 (Feb.) 1958 [Chicago].

The authors present the history of a 53-year-old man in whom an aneurysm of the thoracoabdominal aorta was successfully resected. The aneurysm involved the celiac and superior mesenteric arteries and had ruptured into the psoas muscle. The bypass principle, applied by De Bakey to aneurysms in this location, was modified to achieve minimal periods of visceral ischemia by leaving the aneurysm in situ until most of the permanent anastomoses had been accomplished. The patient whose case is reported appears to be the 5th to have left a hospital well after removal and replacement of an aneurysm in this location, the 1st in whom the aneurysm had ruptured prior to operation, and the 1st in whom a protein-digested bovine heterograft was employed for the temporary bypass shunt.

The aneurysm in this man was dissecting a path into the psoas muscle, like a cold abscess, and his observation of something trickling down his spine during palpation of the aneurysm should have received more careful attention. The protein-digested bovine carotid artery employed for the temporary shunt functioned with complete satisfaction for 4 hours and 40 minutes before it was disconnected. The ready availability of this material and its qualities of ease of handling, nonleaking, and nonclotting make it ideal for this purpose. Whether or not this material will have a place in permanent arterial replacement is beyond the scope of this paper. Papain-digested equine arterial heterografts

have been found wanting in permanent human application, with aneurysmal dilatation as the end-result.

Operative Treatment of Atresia of Esophagus: Results and Complications. T. T. C. Gertz and C. C. Winkel Smith. Danish M. Bull. **5**:18-25 (Jan.) 1958 (In English) [Copenhagen].

Atresia of the esophagus occurs in several forms, the most common of which is that in which the upper segment of the esophagus is united by fistula with the trachea slightly above the bifurcation. The latter type, which is most amenable to operation, was present in 61 of the 67 infants with atresia of the esophagus who were admitted to the pediatric department of the Rigshospital from 1948 to the middle of 1957. Radical operation was performed on 52 patients, with 24 deaths; 3 of the survivors died later. The remaining 25 children are, by and large, developing normally. Since 1951 all operations have been transpleural through incision in the 4th or the 5th intercostal space, which the authors consider the method of choice. Diagnosis as soon as possible after birth is important, with transfer of the infant to a pediatric department and access to surgical treatment as soon as possible. Complications present before the operation include pulmonary complications and such malformations as malformations of the heart. Recurrence of esophageal fistula and leakages suggest that the operative technique may be improved, which is the only means of improving the result.

Suprahyoid Neck Dissection for Epidermoid Carcinoma of the Lower Lip: An Appraisal of Its Use in 130 Patients. A. Klippel and C. Eckert. Am. Surgeon **24**:107-111 (Feb.) 1958 [Baltimore].

Suprahyoid neck dissection was performed on 130 patients with epidermoid carcinoma of the lower lip at the department of surgery of Washington University School of Medicine, in St. Louis, between 1934 and 1948. Of the 130 patients, 40 showed no clinical evidence of lymph node metastasis at the time of the neck dissection. In this group, the neck dissection may be classified as prophylactic. In 4 of the 40 patients, lymph node metastases were detected at the time of the pathological examination, an incidence of 10%, which strikingly parallels the incidence of lymph node metastases in prophylactic neck dissections for cancer of the lip reported by other workers. Clinical evidence of lymph node metastases existed in the remaining 90 patients at the time of operation. In this group, pathological confirmation of the clinical impression was possible in 43 patients. In none of the patients whose primary lesion was controlled and in whom the lymph nodes were considered by the pathologist to be uninvolved was there evidence of cervical lymph node involvement in the course of the 5-year follow-up.

Operative deaths occurred in 2 (1.5%) of the 130 patients. In 10 patients the primary lesion was not controlled by the surgical intervention. Four patients were lost to follow-up. Three patients died of other causes in less than 5 years after the operation, but at the time of their deaths there was no evidence of cancer. In 15 patients persistence of the neoplasm in other portions of the neck was noted at some time after the suprahyoid neck dissection. Thirteen patients were cured, an absolute cure rate of 27.7%. When corrected for the patients in whom the primary lesion was not controlled, or in whom death occurred in less than 5 years with control of cancer up to the time of death, the cure rate was 38.2%. In 12 of the 15 patients with persistence of the neoplasm in the neck, the nodes immediately adjacent to the field of the suprahyoid operation were first observed to be involved. Suprahyoid neck dissection is, therefore, considered to be an unsatisfactory definitive procedure for lymph node metastases from epidermoid carcinoma of the lower lip.

The Intra-Osseous Vasculature of the Distal End of the Humerus with Special Reference to Capitulum. S. Haraldsson. Acta. orthop. scandinav. **27**:81-93 (No. 2) 1957 (In English) [Copenhagen].

The author studied the topography of the intraosseous vascular system in the distal end of the humerus, particularly in the capitulum, on cadavers of persons ranging in age from 3 months to 75 years. A contrast medium consisting chiefly of white lead was injected into the vascular system, and on the basis of the observations the author arrived at the following conclusions: 1. As long as the nucleus of ossification of the capitulum of the humerus lies isolated in the epiphysial cartilage, it appears to receive its blood supply via a few vessels entering the cartilage from behind and forming intercommunicating vessels in the nucleus of ossification. At this stage of development the vessels of the nucleus (of ossification) are not in communication with the other parts of the distal end of the humerus. 2. The nucleus of ossification of the capitulum humeri extends in to the radial part of the epiphysial cartilage of the trochlea. Part of the trochlea is thus ossified from the ossification nucleus of the capitulum. 3. Vessels are seen to extend to the future site of the ossification nucleus (nuclei) of the trochlea before the bone salts deposited there have reached a concentration high enough to be demonstrable in the roentgenogram. 4. The topography of the vascular system forming in the capitulum during the period of ossification persists practically unchanged in the adult bone. 5. After ossification of the cartilage between the

various nuclei of ossification of the epiphysis and of the epiphysial plate, the blood vessels of the diaphysis, metaphysis, and epiphysis intercommunicate.

The Painful Elbow: A New Approach. R. Meyer. Acta med. orient. **16**:262-265 (Nov.-Dec.) 1957 (In English) [Jerusalem].

Patients with painful elbow, men and women of all age groups and occupations, complain of a dull pain in their forearm, especially during certain movements, such as using a screwdriver or lifting a load. When asked to indicate the spot where it hurts, they usually place the elbow in flexion of about 150 degrees, the forearm in pronation and the wrist in ulnar and volar flexion, and point to a site somewhere between the lateral epicondyle and the radial shaft. Some tenderness in the neighborhood of the lateral epicondyle, especially on the radial head, is usually present; passive movements are painful, although seldom restricted; signs of wasting and inflammation are absent. There has been no agreement on either the pathology or the treatment of painful elbow, but Bosworth in 1955 suggested a new type of operation which he came upon by chance. In 2 of his operations undesired accidents had occurred. The orbicular ligament (known also as the ligamentum annulare radii, forming part of the radial collateral ligament, consisting of circular fibers encircling the head of the radius and being inserted in the ulna on either side of the incisura radialis) was cut in operation. In the other the orbicular ligament, released from its attachment to the lateral epicondyle of the humerus, slipped down over the neck of the radius. However, the outcome of the operation was excellent in both patients. Prompt and lasting recovery was the result.

Resection of the orbicular ligament only, without division of the common head of the extensors, appealed to Meyer for the following reasons: 1. The operation releases a tight ligament which is under constant friction in pronation and supination. 2. It acts on the most tender spot. 3. Unlike the division of muscles, it does not weaken the power of dorsiflexion of the wrist needed in forceful closing of the fist. 4. It removes a ligament which is not essential in maintaining stability of the elbow. The author used Bosworth's procedure in 8 patients not responding to conservative treatment. In all of them the pain ceased, although the elbow remained sore for from 1 to 3 weeks. Two patients experienced a slight restriction of active movements, which subsided after 3 weeks without any treatment. The technique of the operation is simple. The author used it only when tenderness was most intense over the radial head. Patients more sensitive to pressure over the lateral epicondyle, as a rule, responded to conservative treatment.

NEUROLOGY & PSYCHIATRY

The Prevention of Chlorpromazine Jaundice. F. Dreyfuss, H. Klein and H. Z. Winnik. Acta. med. orient. **16**:251-254 (Nov.-Dec.) 1957 (In English) [Jerusalem].

Liver damage resulting from the administration of chlorpromazine has occasionally played at least a contributory role in the death of a patient; it has led to unnecessary laparotomies and has at times led to premature termination of well-indicated chlorpromazine treatment. The evidence accumulated so far points to an intrahepatic, obstructive, cholestatic type of liver damage. Since bile thrombi are the predominant feature of the microscopic picture, the authors thought that increased viscosity of the bile might be a factor of etiological importance. They, therefore, attempted to prevent this type of hepatitis by increasing the fluid intake of patients undergoing chlorpromazine treatment. Starting in June, 1955, every patient undergoing chlorpromazine treatment was put on "fluid prophylaxis," that is, about 2.3 liters of sweetened tea or plain water were added to the patient's regular daily fluid intake. The patient usually received 200 mg. of chlorpromazine by injection or 300 mg. by mouth per day. Prior to the period of fluid prophylaxis, 16 cases of chlorpromazine jaundice had occurred among 363 patients undergoing chlorpromazine treatment (4.4%). Only 2 cases of jaundice occurred among the 688 patients treated with chlorpromazine and fluid prophylaxis from June, 1955, to June, 1957, inclusive. The rate of jaundice due to chlorpromazine administration is now less than 0.3%.

Use of Androstenediol in Therapeutic Neuropsychiatric Management. P. Dazzi. Minerva med. **48**:4097-4099 (Dec. 5) 1957 (In Italian) [Turin, Italy].

The current knowledge about androstenediol, whose chemical formula is Δ^5-androstene-3β,17β-diole, is mostly of pharmaceutical nature. The androgenic, estrogenic, and progestational properties ascribed to this drug have led the author to use it in the treatment of a series of 39 women, between the ages of 38 and 62 years, with various disorders of the nervous or psychic systems. The patients were divided into 3 groups. The first group consisted of 16 women with pronounced psychic instability accompanying menopause. The symptoms persisted for several months and did not tend to subside. The patients complained of continual and severe headache, sudden flashes, gastrointestinal disturbances, and insomnia which was unmanageable with common sedatives. Androstenediol was given in weekly doses of 3 vials, each containing 25 mg. of the drug, during the first month; this dose was reduced to 2 vials during the second and third therapeutic months. The patients were kept

under observation for a period of 4 to 8 months. Twelve patients have shown improvement of the objective symptoms. Subjective symptoms, such as lassitude, fatigability, and depression, have subsided more slowly, and required a second course of treatment in the case of 7 patients. The second group consisted of 14 patients in menopause, in whom the common symptoms of the transitional phase were associated with disturbances of the cenesthetic feeling. Psychic examination showed depression, accompanied by hypochondriacal attitude, which was refractory to all psychotherapeutic procedure. Only 8 patients in this group obtained an improvement of objective symptoms. The particular beneficial effect of the drug consisted in correcting the introvert attitude of the patients so as to make them more receptive to psychotherapeutic management. The third group of patients consisted of 9 women, with the type of depression called by Delay "minor." The patients complained of symptoms similar to those of anesthopathia: headache, vertigo, blurred vision, and lassitude. The main symptom was depression, which lasted for short periods of 15 to 20 days. Androstenediol therapy brought the humoral state to normal in 5 patients within 8 months. The remaining 4 patients obtained benefit only at the termination of therapy, which effect vanished within the next 15 days. The author recommends an individualized, rather than a nosographic, procedure in using androstenediol in the treatment of patients with nervous or psychic disorders.

Serological Epidemiology of Poliomyelitis in Central Scotland. R. C. MacLeod, L. G. MacGregor, H. E. Larminie and N. R. Grist. Scottish M. J. 3:76-81 (Feb.) 1958 (In English) [Glasgow].

Single serum specimens were examined for the presence of detectable antibody to the 3 types of poliomyelitis virus in a selected series of 450 children from different areas in central Scotland. It was found that in central Scotland a similar proportion of the children possess antibody to each of the 3 types. The incidence of antibody to all 3 types increases rapidly with increasing age. This finding is in keeping with the age distribution in cases diagnosed in this area, where some 60% occurred in the first 5 years of life and 75% before the age of 10. The similarity in the results obtained with each type of virus has indicated that they are equally prevalent. The paralytic disease appeared with increased prevalence in 1947, 1950, and 1955, but these episodes have not seemed to have left a distinctive mark upon the child population as measured by the age of development of type-specific antibody. Indeed, the similarity of the curves of antibody acquisition for each type and the gradual appearance of increasing immunity in the population surveyed as age advances indicate a widespread prevalence of virus. In children from the higher social levels, antibodies develop at a later age than in children of the lower social grades. The factors that produce this difference seem to be most effective in the early years of life. Analysis shows that this difference is not explained simply by family size and that, indeed, within the family there may be much variation in antibody type.

The State of Natural Antipoliomyelitis Immunity in Children Living in Closed Environments. G. C. Angela, G. Giuliani and W. Grillone. Minerva med. 49:252-256 (Jan. 24) 1958 (In Italian) [Turin, Italy].

Serum specimens were obtained from 148 children, between the ages of 6 months and 4½ years, living in 2 community centers for underprivileged children in Cuneo and Turin, so as to study the state of their natural antipoliomyelitis immunity. A surprisingly high incidence of antibody carriers for poliomyelitis virus was established. Among the 83 infants in the group 6 to 12 months old in Cuneo, 81.8% had antibodies for the virus type 1, and 45.4% for both types 2 and 3. The authors interpret the high incidence of natural immunity among the youngest infants as a result of a process of immunization related to a more intense outbreak of the epidemic of poliomyelitis which occurred in Cuneo at the time the infants were born. Since these children came from poor homes, they probably had been exposed to the influence of the virus during the epidemic and had thus acquired the natural immunity. The lower incidence of natural immunity among the older groups was probably due to the fact that these children had lived in the community centers for a while and had not been exposed to the virus which was rampant in the outside world. The incidence of natural antipoliomyelitis immunity in 65 children in the community center in Turin differed somewhat from that observed among the children in Cuneo; 33% presented no antibodies, 42.8% had antibodies for the virus type 1, 47.6% for type 2, and 57.1% for type 3. In the group 3 to 5 years, only 54.5% of the children had antibodies against all 3 types of poliomyelitis virus. The opinion of the authors is that life in a closed, selected environment impedes the acquirement of natural antipoliomyelitis immunity. The best protective measure for these children is the antipoliomyelitis vaccination.

Generalized Moniliasis with Localization in the Brain. J. Eschwege. A. M. A. Arch. Neurol. & Psychiat. 79:250-263 (March) 1958 [Chicago].

The author reports the case of a 21-year-old man who for 8 days before hospitalization had increasing headaches, joint and muscular pain, and temperature up to 39 C (102.2 F) and who was admitted to hospital with a diagnosis of poliomyelitis.

On admission he appeared slightly somnolent, and pronounced rigidity of the neck was present. Examination of the cerebrospinal fluid showed the following findings: 24 cells per 3 cu. mm., all mononuclears; protein, 41.8 mg. per 100 cc.; glucose, 72 mg. per 100 cc.; pressure, 165 mm. of water; and positive reactions to the Pandy and Nonne tests. The cerebrospinal fluid was at first clear and colorless but later became cloudy and xanthochromic. The patient was treated extensively with various antibiotics. Within 11 days he was given a total dose of 16 Gm. of chlortetracycline (Aureomycin) orally, which lowered the temperature to subfebrile values, but his condition deteriorated. Thereafter, treatment was continued with streptomycin, 19 Gm. administered intramuscularly and 150 mg. intrathecally, in combination with 14.5 Gm. of isoniazid administered orally and 6.4 Gm. intramuscularly because of a suspected tuberculous meningitis. The penicillin received by the patient totaled 11 million units given intramuscularly. Fifteen days after admission the patient was in coma, and a tracheotomy was performed because of superficial respiration and beginning cyanosis. Twenty-four days after admission the patient, previously constipated, discharged increasing amounts of liquid, often bloody stools, an indication of beginning ulcerative colitis. This was about 1 week after the administration of chlortetracycline was discontinued. More and more the patient began to present the picture of decerebrate rigidity. He died of circulatory failure after 1 month of hospitalization.

The exact nature of the underlying disease, with symptoms and signs referable to an inflammatory process affecting the meninges and the brain, for which the patient had been admitted to the hospital, could not be ascertained in life. All tests for tuberculous meningitis, including 3 animal experiments, gave negative results. The histological findings showed no evidence of a tuberculous process, the signs of which might have been suppressed by the streptomycin and isoniazid therapy. The bacteriological and viral examinations, as well as agglutination tests, including those for leptospirosis and toxoplasmosis, also were negative. Oral thrush was never found in the patient. The cerebral changes observed at autopsy were of 4 types: (1) metastases, characteristic of thrush (Candida albicans), all surrounded by glia-cell nodules of varying sizes, principally but not exclusively in the gray matter of the entire brain, with sites of predilection in the medulla oblongata and the basal ganglions, the thalamus, and the cortex of the temporal regions; (2) perivascular lymphocyte and plasma-cell infiltrations, not directly dependent on the nodules but more frequent in these nodule areas; (3) extensive areas of relatively increased and hypertrophied astrocytes and microglia cells in the gray, and more seldom in the white, substance, not directly correlated with the nodules; and (4) severe dementia-paralytica-like destruction and reaction centers in a closely circumscribed temporal region. These findings differ from those in the other so-called metastatic focal encephalitides of viral or bacterial origin in the larger size of the granulomas and the more extensive destruction of the nerve parenchyma in isolated areas of the cerebral cortex. Microscopically, a fungus identified as Candida was demonstrated in foci located in the peripheral musculature, the myocardium, the colon, the kidneys, and the brain. Macroscopically, there existed a severe ulcerative colitis. Every mycotic infiltration which ulcerates and comes in contact with the blood stream may lead to a hematogenous dissemination of the fungus, and there is little reason to doubt that the colon was the point of origin for the dissemination of the mycosis.

Since the broad-spectrum antibiotics have been generally employed, there has been a sharp rise of generalized moniliasis, especially of forms affecting the central nervous system, due to the destruction of the antagonistic intestinal flora which had inhibited the growth and proliferation of the fungus. The diagnosis of these forms of generalized fungus infection has been difficult, owing in part to inaccuracies inherent in the diagnostic methods and in part to the lack of familiarity of most physicians with these diseases, and also because of their clinical symptoms which fit other inflammatory diseases of the brain or meninges. Good antifungal agents, such as nystatin, are available and, when given in conjunction with broad-spectrum antibiotics, may do much to prevent or control a generalized Candida infection. Despite this, the prognosis of manifest generalized moniliasis remains grave. The indiscriminate use of antibiotics without the proper indications must, therefore, be avoided.

PEDIATRICS

Hyperadrenocorticism in Children, Due to Adrenocortical Adenoma: Study of a Case of Postoperative Cure Persistent After Six Years. R. Turpin, F. de Gaudart D'Allaines, R. Gorin and P. Thibault. Semaine hôp. Paris **34**:210-220 (Jan. 24) 1958 (In French) [Paris].

The authors report the case of a 5-year-old girl with a hyperadrenocortical syndrome due to an adrenocortical adenoma. On admission to hospital the child had hirsutism, moderate obesity of the face and trunk, and considerable hypertrophy of the external sex organs, particularly the clitoris. She also had arterial hypertension and a relative slowing of body growth. There was increased excretion of 17-ketosteroids in the urine (4.9 mg. within 24 hours), while that of the 11-oxysteroids (formaldehydogenic steroids) was almost normal. Signs of hyperactivity of the pituitary gland and of the ovaries were absent. The retropneumoperi-

toneal roentgenologic examination revealed an enlarged right adrenal gland; the left adrenal gland was normal. The child was operated on, and an adrenocortical adenoma with spongiocytic differentiation and relatively reduced lipid content was removed. The extirpation of this benign tumor was followed by the restoration of the arterial pressure to normal, and the obesity disappeared. Hirsutism was reduced, but an abnormal amount of pubic hair and hypertrophy of the clitoris and of the labia majora persisted. There was a pronounced acceleration of body growth, 14 cm. (5.5 in.) within 1 year after the operation. The excretion of hormones in the urine was restored to normal. The child was reexamined once more at the age of 10 years and 8 months. Beginning of the menstrual function had occurred a few days before this examination. The weight of the child was 38.5 kg. (85 lb.), and her height was 149 cm. (4 ft. 11 in.). There was axillary hair and the development of the breasts appeared to be normal for the age of puberty. The arterial pressure was normal (120/70 mm. Hg) and the general condition excellent. Her school record was good, although she was retarded by 1 year because of her previous disease. She was considered completely cured.

The adrenal origin of the syndrome in this patient is evident. Hyperadrenocorticism occurring before the age of 10 years in a previously normal child is almost always due to an adrenal tumor which is generally malignant. The benign tumor in the patient whose case is reported is an exception. In patients over 10 years of age the incidence of benign tumors increases. The excision of the tumor, which resulted in a complete cure in this case, made it possible to observe a gradual return to a normal endocrine balance and particularly to analyze some definite disturbances in body growth which were only of secondary interest before the operation. Hirsutism and hypertrophy of the clitoris were manifestations of a moderate hypersecretion of androgens, as confirmed by the increased excretion of 17-ketosteroids without increase in the β-fraction of these steroids. The hypersecretion of androgens should have had a stimulating effect on the body growth and the maturation of the bones, but since this was not the case, it must have been counterbalanced by an antagonistic hormone secretion. It is suggested that the adrenal glucocorticoids played the part of this antagonistic hormone, exercising a preponderantly inhibitory action on the patient's body growth by their catabolic or protein-antianabolic effect. This latter effect also favored an increased production of carbohydrates and their transformation into fats, which may explain the moderate but definite degree of obesity. The hypertension may have been attributable to the excess in mineral corticoids or may have depended on the hypersecretion of glycoprotein hormones. The occurrence of this viriligenic adrenal tumor in a female patient less than 10 years old is noteworthy.

Staphylococcus Pneumonia in Childhood. J. Kringelbach and J. Winge. Ugesk. læger **120**:143-150 (Jan. 30) 1958 (In Danish) [Copenhagen].

Staphylococcus pneumonia occurs most frequently during the first 3 months of life. The mortality is considerable. Two main types are described: (1) an acute fulminating type, often fatal after a few days, and (2) a more prolonged and less malignant form which does not react to sulfonamide preparations or penicillin. During the course of the latter type empyema or pneumothorax develops, possibly with tension or pyopneumothorax. Roentgenologic examinations show infiltrations, frequent atelectases, and pneumatocele formation. The diagnosis is suggested by the clinical course and may be verified by culture from the lungs or pleurae. Plasma-cell pneumonia is especially to be considered in differential diagnosis. Treatment consists in administration of tetracycline preparations, use of oxygen, and gastric aspiration; pleural complications are treated surgically. Among the 228 patients with pneumonia treated in the pediatric department of the Copenhagen County Hospital in Gentofte from 1955 to March, 1957, there were 13 cases of staphylococcus pneumonia or empyema, 11 of them in infants less than 1 year old. Of the 6 deaths in the entire series, 3 occurred in infants less than 4 months of age.

UROLOGY

A Physiological Approach to Bladder Irrigation in Gross Hematuria. J. U. Schlegel, H. Jørgensen, A. McFadden and W. W. Scott. J. Urol. **79**:224-229 (Feb.) 1958 [Baltimore].

Bleeding from the urinary tract can create a problem in management, since clot formation may block an indwelling catheter or even a normal urethra. Gross hematuria is quite common after prostatectomy, and it is a frequent postoperative procedure to use continuous or frequent bladder irrigation to maintain the patency of an indwelling catheter by diluting the blood sufficiently to avoid clotting. Such a procedure has several disadvantages. There is the danger of inducing an infection, accurate urine volume is hard to estimate due to the presence of a large amount of irrigation fluid, and frequent attendance to maintain the patency of the catheter is required. Many of these disadvantages could be overcome if a diuresis of sufficient volume could be established to maintain an internal irrigation. However, attempts to hydrate patients after surgery, as well as during conditions involving pain, hemorrhage, and emotional dis-

turbances, will result in overhydration, with retention of fluids, due to antidiuresis. It is known that during antidiuresis the urine volume is directly related to the amount of solutes excreted. Urea is a solute which apparently is utilized rather passively by the kidney and which will be distributed evenly over total body water, thus not causing any change in the compartmental distribution.

It had been shown by the authors that antidiuresis after surgery can be completely overcome by the administration of urea as a 4% solution. In this paper, they present a practical utilization of the basic physiological phenomenon of post-traumatic antidiuresis in 40 patients who had been subjected to prostatectomy. They found that in patients for whom 4% urea is added to infusion solutions of 5% dextrose in water, there is, in general, no change in the serum electrolytes, as compared with patients receiving approximately 2,000 cc. of intravenously administered fluids in the form of 5% dextrose in water and no urea added. This holds true even with fluid intakes as high as 4,000 cc. in the 24-hour period immediately after surgery. The administration of urea did not change the excretion of sodium. The authors conclude that the addition of 4% urea to the standard dextrose infusion makes possible the administration of large fluid volumes without the risk of water intoxication. The increased urinary output thus obtained appears to be a valuable aid in the management of patients after suprapubic prostatectomy. Recently the authors utilized the principles described in other cases of gross hematuria with equal success.

Dissolution Treatment of Vesical Calculi by Means of Automatic Irrigation Device. P. O. Hösli. Helvet. chir. acta **24**:595-603 (Dec.) 1957 (In German) [Basel, Switzerland].

The author discusses the structure of urinary calculi and classifies them according to their composition, taking into account certain clinical factors. He suggests that in some cases an attempt can be made to dissolve the calculi. Vesical stones, especially the so-called struvit calculi, consisting chiefly of magnesium ammonium phosphate (or "triple phosphate") may be treated by continuous irrigation. Poor results of attempts at dissolving calculi have been due mostly to technical difficulties. It is not easy to comply with the demand for an uninterrupted, intensive, and prolonged contact between a constantly renewed irrigation fluid and the concrement. Intermittent irrigation with a syringe is inadequate, and even the use of a double-barreled catheter with continuous irrigation will generally fail, because the stone is not sufficiently surrounded by the dissolving fluid.

The author presents a diagram of an irrigating system constructed by him. It insures, with little supervision, an automatic intermittent flow, and the equipment required is available in any hospital. Several factors, such as the number of drops per minute, the elevation of the container for the irrigating fluid, the threshold, and the position of the discharge vessel, are variable and can be changed. Thus, the number of irrigations per hour may range from 3 to 20, and the amount of fluid per irrigation from 20 to 150 cc. The catheter must be of a large caliber in order to avoid leakage. The author presents the history of an 8-year-old girl in whom this method of irrigation was used successfully. Irrigation was carried out during the first phase with 3% boric acid solution and later with G solution, but the author believes that the choice of fluids was not decisive. Three to four irrigations were given per hour with from 30 to 40 cc. of fluid.

The Hospital Urine Bottle and Bedpan as Reservoirs of Infection by Pseudomonas Pyocyanea. J. W. McLeod. Lancet **1**:394-397 (Feb. 22) 1958 [London].

There is evidence that endemic persistence of Pseudomonas pyocyanea on surgical wards may be responsible for much of the infection of this kind which often follows catheterization and operations on the urinary tract. Such infections have been reported in hospitals in many different parts of Britain. Certain wards, apparatus, and personnel of 3 hospitals in which Ps. pyocyanea infection had been observed were systematically examined. Similar investigations were also made, insofar as they were pertinent, in the laboratory in which the work was being done, to check the possibility that accidental laboratory contamination might be responsible for some of the observations made. In each of the 3 hospitals there was an outstanding type of Ps. pyocyanea strain differing from those in the 2 others, both in its reactions to agglutinating serums and in its bacteriophage sensitivity. It appears that infections with Ps. pyocyanea are largely hospital infections. This bacterium easily adapts itself to the human urinary tract, especially in the presence of protein exudate such as must inevitably be present after operations on the bladder. It is not a commensal organism of the normal external genitalia of the male and is not therefore unavoidably introduced in such procedures as catheterization. It does not readily persist in the dry state and is only found in dust exposed to recent heavy contamination.

The apparatus in normal ward use in which it can most readily persist is the urine bottle and the bedpan. Evidence was obtained that nurses and orderlies required to empty and rinse urine bottles and bedpans on urologic surgical wards will inevitably infect their hands repeatedly with Ps. pyocyanea. Hence, they are a source of danger to any patient whose bladder and drainage or lavage apparatus they have to manipulate. It seems prob-

able that much of this infection could be avoided by a proper use of antiseptics. This would involve storing in an antiseptic tank all urine bottles and bedpans not in use and issuing bottles for use only from such tanks. If there was in each bottle a residuum of antiseptic solution—about a fifth of the capacity of the bottle, it would be sufficient to sterilize the bacteria excreted by the patient even when diluted fourfold by urine.

The sterilization of the feces by residual antiseptic in the bedpan is more difficult, but the danger of infection from this vessel could be largely eliminated if 2 procedures were regularly followed. The first of these would be sterilization of the bedpan, after cleansing, by a brief immersion in boiling water or a longer one in an antiseptic bath. The second would be that the nurse or the orderly handling bedpans should do so only when wearing rubber gloves; if the gloves, while still on the hands, were cleansed under running water and then rinsed with alcohol or, better, an antiseptic solution before they were removed, the contamination of hands would be reduced to a minimum. Complete destruction of bacteria, such as Proteus organisms and Ps. pyocyanea, in a few minutes is not easily attained with any antiseptic. Elimination of infection in all vessels used for the collection of excreta should be assured by an efficient use of antiseptics, as described above. While some antiseptics are not bactericidal for Ps. pyocyanea, phenol (carbolic acid) in a 2% solution is adequate and cheap.

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OPHTHALMOLOGY

Clinical and Etiologic Evaluation of an Epidemic of Keratoconjunctivitis. A. Kahán and I. Béládi. Ophthalmologica **135**:79-87 (Feb.) 1958 (In English) [Basel, Switzerland].

An epidemic of keratoconjunctivitis involved 234 patients who were treated at the clinic of ophthalmology of the medical school of the University of Szeged, Hungary, between 1954 and 1956. In the beginning of the epidemic, clinical manifestations consisted of multiple, grayish, subepithelial lesions of the cornea, sometimes associated with a central epithelial defect and accompanied by mild conjunctivitis but without adenopathy or any general symptoms; in some patients, these foci were located near the limbus, with engorged vessels and even with the appearance of a small pannus. Most of the patients were middle-aged, being 35.3 years old on the average. From April, 1956, onward there was a change in the clinical aspect, and a conjunctivitis, characterized by many petechiae near the lid margin and associated with pharyngitis and general symptoms, predominated. The patients were young people and children, the average age being 24.4 years. In this aspect of the disease the cornea was involved only in adults, but the disease was associated with simultaneous herpes eruptions in children. From 2 patients with conjunctivitis, virus strains were isolated on HeLa-cell cultures; these were identified as type 3 of the adenovirus group, and specific neutralizing antibodies were found in the patients' serums. The epidemic culminated in August-September, 1956; a chlorinated swimming pool was suspected as chiefly contributing to the spreading of the disease. Jawetz' hypothesis that the cases of conjunctivitis occurring in the outbreaks would be caused by an adenovirus and that involvement of the cornea would occur only in patients with coexistent herpes infection is supported by some of the data reported by the authors.

Septic Retinitis Due to Candida Albicans. J. M. Van Buren. A. M. A. Arch. Path. **65**:137-146 (Feb.) 1958 [Chicago].

Mycotic infection of the eye by any route is rather rare, but there have been instances of conjunctival infection with Candida albicans. The present case was considered of interest because in a patient with a blood-stream infection with C. albicans a small retinal lesion resembling a Roth spot appeared; at postmortem examination this lesion was found to contain the hyphal elements of the yeast. The increase in recent years in recorded instances of systemic moniliasis suggests that further examples will come to light. The patient presented was a 53-year-old woman, in whom a diagnosis of multiple myeloma had been established 12 months previously. A retinal lesion was noted several months after C. albicans had been cultured from the vagina and the patient had had a mild but prolonged attack of enteritis. There was also a history of recent head injury, and for an attack of pneumonitis the patient had been treated with penicillin and streptomycin. Later C. albicans was cultured from the urine, the blood, the throat, and the bone marrow. The retinal lesion at this time lay above the disk, about a disk diameter from its margin, and consisted of a rounded hemorrhagic area, the center of which was white. The lesion was apparently uninfluenced by the pattern of the nerve-fiber layer and was not in relationship to a blood vessel. In the next few days there was enlargement by inferior and lateral extension. It was suggested that this might be a local C. albicans colony in the retina. Therapy with nystatin (Mycostatin) was cautiously attempted, but the patient proved intolerant to the medication. The patient's subsequent course was complicated by femoral thrombophlebitis and continued pneumonitis. Death preceded by an acute substernal pain occurred a month after the discovery of the retinal lesion.

Microscopic studies on the eyes during the postmortem examination indicated that the major retinal lesion had evidently taken origin in the nerve-

fiber layer, and hyphal and budding forms of the yeast were demonstrated in one lesion. An additional type of retinal lesion was seen in which there was little, if any, evidence of inflammatory reaction. Two types of retinal lesions have been found, both in the present case and in previous cases of bacillary septicemia and embolism. Both types of lesions arise in the nerve-fiber layer, but the reason for the apparently exclusive origin in the nerve-fiber layer is not clear. One type of lesion is frankly inflammatory and seems adequately explained as a result of a septic embolus. The second type, perhaps more properly termed a Roth spot, is a more localized lesion, the response to which is predominantly noninflammatory. Difficulties are pointed out in accepting the latter lesion as being due to embolism, infarction, or varicose axonal degeneration of the retinal ganglion cells.

OTOLARYNGOLOGY

Deafness Following Mumps. G. Everberg. Acta oto-laryng. **48**:397-403 (Nov.-Dec.) 1957 (In English) [Stockholm].

The author reports on 112 children and adolescents, with total deafness in one ear and clinically normal hearing in the other, who were studied at the ear clinic of the City Hospital in Copenhagen. Sixty-five of these patients had a history of mumps. In 44 the mumps had occurred before the deafness was recognized, but in only 5 could the deafness be reasonably attributed to mumps. These 5 cases of deafness due to mumps were detected among a population of 185,000 examined over a period of 10 years. Within the same period and within the same area, no case of bilateral deafness was found after mumps. Half of this population had a history of mumps, and, therefore, the frequency of deafness as a complication to mumps may be estimated to be about 0.05 per thousand. A review of the literature has revealed that 80% of all cases of deafness due to mumps may be estimated to be unilateral.

Malignant Melanoma in Rhinopharynx and Nasal Cavity. B. W. Walther. Nord. med. **59**:145-147 (Jan. 23) 1958 (In Danish) [Stockholm].

Malignant melanoma in the rhinopharynx and the nasal cavity has not often been described in Scandinavian literature. The diagnosis, while simple, is frequently not made primarily. Usually evulsion of nasal polypi is done several times without suspicion of malignancy. On pathanatomic examination because of rapid recurrence, sometimes with black-colored tumor masses, nosebleed, headache, and metastases, malignant melanoma is diagnosed. Most authors recommend routine pathanatomic diagnosis of all nasal polypi. Urine reaction to melanogen does not, as a rule, become positive until there are large tumor masses and extensive metastases. As radical an excision as possible regardless of postoperative cosmetic defects, with electrocoagulation as supportive technical help, is the only form of therapy which, applied at an early stage, offers the possibility of recovery. Radiotherapy and radioactive substances are only palliative. The prognosis is poor; about 5% of the patients are expected to survive from 2 to 5 years. However, with today's improved technique and radical excision at an early stage, improvement in the prognosis may be looked for. The personal case reported was that of a farmer, aged 60 years, who had been treated several times from 1947 on for chronic hypertrophic rhinitis, deviation of the septum, and rapidly recurring nasal polypi. Pathanatomic diagnosis of malignant melanoma was made in 1948. The melanoma was treated by electrocoagulation and excision. The patient's condition remained remarkably good except for repeated local recurrences that were treated by palliative electrocoagulation. Operation for acute ileus in 1953 revealed invagination of the small intestine due to metastasis from the rhinopharynx melanoma. A year later metastasis to the liver was palpated. After the establishment of the malignant melanoma, the patient lived more than 6 years and continued to do light farm work until a few months before his death. He lived 15 months after the first sign of distant metastasis.

584 Foreign Bodies Removed from the Esophagus: A Statistical Study. E. S. Ray and P. P. Vinson. Virginia M. Month. **85**:61-64 (Feb.) 1958 [Richmond].

In the course of 20 years the authors directed the treatment of 933 patients who had foreign bodies in the air or food passages. This report is concerned with the 584 in whom the foreign body was in the esophagus. Contrary to the general belief, foreign bodies are found in the esophagus more frequently in adults than in children. Of the patients whose records were reviewed, 269 were under 10 years of age, while 315 were 10 years of age or older. The youngest patient was 2 months old, and the oldest was 94 years. The absence of teeth is a major factor in the impaction of a foreign body in the esophagus. In adults inadequate mastication and the loss of sensation in the mouth that results from artificial dentures is responsible for bones and meat sticking in the esophagus. Dentists should warn all patients, when they are provided with partial or complete dentures, of this hazard and should explain that care should be taken in the preparation and mastication of food. This applies particularly to chops, hash, and especially to chicken served à la king, in a salad, and in a pie. The authors also take issue with dentists who recommend that removable dentures, complete or

partial, be left in a patient's mouth during sleep. Several of the patients swallowed dentures while they were asleep.

Foreign bodies most frequently lodge in the upper third of the esophagus. Painful deglutition and obstruction to passage of food through the esophagus are the most frequent symptoms. The majority of foreign bodies are not revealed by roentgenoscopy, and diagnosis must be made from history and esophagoscopy. When a foreign body that is nonopaque to x-rays is suspected in the esophagus, barium should not be used as a contrast medium in localization, but iodized oil may be employed. Esophagoscopic examination should be made without delay. General anesthesia increases the comfort and safety of instrumentation. Preexisting lesions in the esophagus are frequently responsible for lodgment of a foreign body, especially in the lower third of the organ. Whenever a foreign body is encountered in this location, the esophagus should be thoroughly examined after removal. Impaction of a foreign body, especially a bolus of meat, at the site of a previously existing stricture may further compromise an already reduced blood supply and may result in necrosis and rupture of the wall of the esophagus. Dilation of a stricture should be deferred for at least a month after removal of a foreign body to permit healing of ulceration and reestablishment of circulation. A foreign body that passes through the esophagus will usually continue through the gastrointestinal tract and be expelled spontaneously. Occasionally passage through the stomach is delayed, but surgical removal is seldom necessary.

Bronchoscopy in Hemoptysis. F. O. Segarra. New England J. Med. **258**:167-170 (Jan. 23) 1958 [Boston].

The correlation between hemoptysis, roentgenologic picture, and bronchoscopy was studied in 675 patients presenting hemoptysis and abnormal chest films. With the aid of bronchoscopy, the lesion responsible for hemoptysis was discovered in 498 cases (73%). Among the patients with a positive bronchoscopic diagnosis, bronchial cancer was present in 39%, bronchitis in 25%, and endobronchial lesions produced by peribronchial lymph-node calcification in 15%. There is no characteristic roentgenologic picture to give one an indication of the bronchopulmonary disease responsible for the hemoptysis, with the exception of the peribronchial lymph-node calcification and the pulmonary retractions, in which bronchoscopy reaches the highest figures of positivity. Formerly, when the x-ray study failed to give an answer, the problem could be explained by the assumption of the existence of bleeding in the larynx or the pharynx. The present study shows that this view is no longer tenable. The usefulness of the bronchoscopic method stands out clearly if one considers that in 73% of all the cases of hemoptysis, regardless of whether or not they were associated with roentgenologic abnormalities, it was possible to localize the bleeding point in the bronchi. The routine performance of bronchoscopy in patients who have expectorated blood is advised regardless of the results of roentgenologic examination.

THERAPEUTICS

Arterial Embolism Occurring During Systemic Heparin Therapy. R. E. Weismann and R. W. Tobin. A. M. A. Arch. Surg. **76**:219-227 (Feb.) 1958 [Chicago].

Heparin is considered to be a valuable and effective anticoagulant agent. During recent years, concomitant with a more aggressive medical and surgical management of the various vascular disorders, the authors observed and treated a number of patients who suffered major arterial embolism while receiving heparin. The increasing frequency of this complication induced them to study this phenomenon. They present 10 patients in whom 1 or more emboli occurred during the systemic administration of therapeutic doses of heparin. In some patients the embolization nullified an apparently satisfactory result of the initial medical or surgical treatment. Embolectomy was performed in all patients. Clinical and autopsy studies suggested that all patients had occult friable aortic thrombi, in various states of unstable organization, which were not suspected or recognized prior to the sudden dramatic peripheral occlusion. The embolizations observed in these 10 patients were from the aortic wall and were precipitated by some unknown local effect of systemic heparinization. The gross and microscopic characteristics of the emboli collected at operation were the same in all cases in this group. Arterial embolism must be considered a possible complication of vigorous heparin therapy in those persons with preexisting aortic thrombi.

Acetazolamide in the Treatment of Chronic Cor Pulmonale. P. Longo. Minerva med. **49**:84-91 (Jan. 13) 1958 (In Italian) [Turin, Italy].

Sixteen hospitalized male patients with cor pulmonale received acetazolamide therapy, supplemented by the administration of nicotinic acid, antibiotics, and digitalis or strophanthus. The bronchopulmonary disorders were mostly of emphysematous and, in some instances, of sclerotic or pneumoconiotic types. At admission the patients had cyanosis, hepatomegaly, distended neck veins, and edema. Acetazolamide was given in the form of tablets in daily dosage of 500 mg. divided into 2 equal doses during the first 3 days; the dosage was reduced by one-half during the succeeding 5 to 10 days. After a short drug-free period, the therapy was resumed in daily dosage of 250 mg.

The most important effect of acetazolamide was a marked diuretic action, which was observed in all but 3 patients. The urinary output increased 2 to 4 times (up to 9 liters), as compared with the initial state, and generally reached its maximum during the first 3 days of the drug therapy. These values decreased slowly afterwards but did not drop during the following 12 to 15 days after withdrawal of acetazolamide below the daily average of 1,500 to 2,000 cc. Diuretic action was retarded in 5 patients until circulatory compensation was attained. Inhibition of carbonic anhydrase was another property of acetazolamide observed in this series of patients. This effect occurred independently of the state of the renal tubules; for this reason, acetazolamide is less nocuous than other carbonic anhydrase inhibitors. This drug also caused a diminution of the partial pressure of carbon dioxide, which process improved the respiratory function. Other beneficial effects were improvement of cyanosis, decrease of dyspnea, and relief from chest stiffness and diaphragmatic pressure. No undesirable side-effects of acetazolamide therapy were observed, except that 1 patient had diarrhea and intestinal upsets a week after the therapy began.

Further Experiences in the Use of Tolbutamide (D 860) in Diabetes Mellitus. T. Schneider, S. Lopis and W. M. Politzer. South African M. J. **32**:149-153 (Feb. 8) 1958 [Cape Town].

Discussing oral substitutes for insulin, the authors point out that the use of carbutamide has been largely discontinued because of its toxic effects; it has been superseded by tolbutamide, known also as D 860. This paper is concerned with experiences with tolbutamide in treating 105 patients attending the diabetic clinic of the Johannesburg General Hospital. The patients were selected as being especially suited for tolbutamide therapy. There were 17 men and 88 women, ranging in age from 43 to 84 years. The duration of diabetes had varied from 2 months to 30 years, and the age of onset from 36 to 75 years. During the course of the investigation these patients attended the clinic regularly for periods of up to 1 year. They were instructed to test their urines for sugar with Benedict's solution 4 times daily (before each meal and at bedtime). They were told to report immediately if any untoward symptoms occurred (sore throat, rash, or temperature) or if urine tests were unsatisfactory.

The dosage of tolbutamide did not exceed 3 Gm. daily. A dose of 3 Gm. was employed on the first day, and this was decreased by 0.5 Gm. per day until a maintenance dose of 1.0 to 1.5 Gm. daily was reached. Initially, the total daily dose was given before breakfast each morning; but later on, as several patients experienced hypoglycemic symptoms of giddiness and headache during the morning, the plan adopted was to administer the drug in 3 equal doses either before or after meals. Where the previous dose of insulin did not exceed 20 units, insulin was withdrawn on the day that tolbutamide therapy was instituted. Where the dose exceeded this amount, insulin was gradually withdrawn by reducing the dose by 5 to 10 units per day. If symptoms and signs of ketosis appeared during this regimen, tolbutamide was withdrawn and the patient restabilized on insulin. Blood cell counts, prothrombin indexes, liver function tests, and blood urea estimations were carried out at frequent intervals.

Evaluating the efficacy of tolbutamide treatment, the authors classified their results as good, fair, and poor. Good control was achieved in 45 patients; fair control in 25; and poor control in 35. Deterioration in control occurred in 8 patients after several months of tolbutamide therapy. Of 7 of those in the good category, 5 deteriorated to fair control and 2 to the poor category, while 1 patient under fair control regressed to the poor category. There were several patients who felt so well while receiving tolbutamide, despite poor diabetic control, that they refused to discontinue taking the drug. Insulin, therefore, was added to improve the control, but the dose was usually less than that previously required. Only minimal side-effects, none of them toxic, were observed as the result of tolbutamide therapy. A temporary reversal of the neutrophil/lymphocyte ratio was found in 37 cases. It is premature to speculate on the effect of tolbutamide in preventing the late manifestations of diabetes. This will require careful follow-up studies over many years and comparison with insulin-treated patients.

The Metabolic Effects of a New Substituted Steroid, 2-Methyl-9-α-Fluorohydrocortisone, in Man. K. J. Gurling, M. B. R. Gore and D. N. Baron. J. Endocrinol. **16**:304-309 (Feb.) 1958 [London].

It has been demonstrated that certain substituted analogues of hydrocortisone possess enhanced metabolic activity; for instance, it was found that 9-α-fluorohydrocortisone had greater electrolyte-controlling and glucocorticoid properties than hydrocortisone itself. The subsequently synthesized analogues with a methyl group in the 2 position, including the halogen-substituted 2-methyl-9-α-fluorohydrocortisone, had greater glucocorticoid and mineralocorticoid activity than hydrocortisone. Animal experiments demonstrated that 2-methyl-9-α-fluorohydrocortisone is the most active electrolyte-controlling steroid so far available in that it causes sodium retention, potassium loss, and depression of the plasma level of 17-hydroxycorticoids; it has greater metabolic activity than aldosterone. This paper describes the investigation of the mineralocorticoid and adrenocortical-suppressing effects of 2-methyl-9-α-fluorohydrocortisone in 4 normal adults. A single oral dose of 0.1 mg. of 2-methyl-9-α-fluorohydrocortisone lowered the uri-

nary sodium/potassium ratio, causing sodium retention and potassium loss. There was an eosinophilia and a fall in plasma 17-hydroxycorticoids and in urinary 17-oxosteroids and 17-hydroxycorticoids. These effects lasted 24 to 36 hours, after which time there was a sodium diuresis and the values returned to normal. Doses of 0.3 mg., repeated for 3 days, enhanced these effects, with accompanying edema and hypokalemia. No significant effects on carbohydrate or protein metabolisms were observed.

The authors show that their observations agree with those of other investigators who found 2-methyl-9-α-fluorohydrocortisone to be 2 to 3 times as potent as aldosterone in its sodium-retaining effect and 3 to 5 times as great in its ability to reduce potassium loss. In view of the rapidity and severity of these electrolyte changes, caution is necessary during its administration. The risk of hypokalemia is particularly great when doses of more than 0.1 mg. of 2-methyl-9-α-fluorohydrocortisone are repeated. It has been suggested that the introduction of the methyl group delays metabolic inactivation, so that the effect on the renal tubules is prolonged. The additional presence of fluorine in the 9-α-position seems to potentiate this tubular effect. The reduction in urinary steroid excretion and the fall in plasma steroid levels appear to be due to suppression of anterior pituitary function and reduction in corticotropin secretion. It has been pointed out that this effect may facilitate metabolic investigations on exogenous adrenal steroids. The small amount of 2-methyl-9-α-fluorohydrocortisone necessary to maintain the condition of the adrenalectomized patient or to depress endogenous adrenocortical hormones is unlikely to be detectable in plasma or urine by existing chemical methods of estimation. The potential therapeutic effect of "medical adrenalectomy" is of interest, but any advantages over cortisone and prednisone in this respect must be weighed against the dangers of electrolyte imbalance.

Phenylbutazone in the Anti-Inflammatory Management of the Tuberculosis of Lymph Nodes. N. De Pasquale, G. La Rosa and N. Puglisi. Riforma med. 72:89-93 (Jan. 25) 1958 (In Italian) [Naples].

Phenylbutazone therapy was tried in 10 patients, between the ages of 15 and 40 years, with various types of tuberculosis of the lymph nodes, mostly in the neck. There were no signs of ulceration or fistulization. The disease had appeared from 2 to 12 months before this therapy began. Most of the patients had previously received other forms of tuberculous chemotherapy. The general condition of health was good in all patients excepting 1 in whom a mild febrile state persisted. A daily oral dosage of 600 mg. to 1 Gm. of phenylbutazone was administered to the patients for 1 week. Two patients each received 2 additional courses of the same therapy. Marked objective improvement, consisting in a decrease of tumefaction and subsidence of fever, was observed in all patients. This was accompanied by a rapid subjective improvement of symptoms. The best amelioration was observed in patients in whom the disease was of recent date and the caseous process dominated the picture. Local anti-inflammatory action was the most important therapeutic effect of phenylbutazone in this series of patients. Completion of this step probably enhances the efficacy of the succeeding specific antituberculous therapy.

PATHOLOGY

Occlusive Disease of the Abdominal Aorta: Structural Alterations. B. Halpert, E. E. Erickson, M. E. De Bakey and others. A.M.A. Arch. Path. 65:158-165 (Feb.) 1958 [Chicago].

Thrombotic occlusive disease of the abdominal aorta is now treated by resection and replacement with vascular substitutes. This study is concerned with the structural alterations observed in the surgically excised segments of 45 abdominal aortas. All resected specimens included the bifurcation of the aorta, with segments of varying length of the common iliac arteries. All patients were men, who ranged in age from 33 to 66 years. The occlusion of the aorta was clinically complete in 26 patients and incomplete in 19. Among those with incomplete occlusion, the common iliac artery on the right or on the left was completely occluded in 9. The occlusive process was due to atherosclerotic change in the walls of the aorta and the common iliac arteries. Several case histories are described to illustrate the clinical manifestations, operative treatment, and structural changes in the resected vessels. It was observed that the alterations, atherosclerotic, calcific, and bone formation, with a constant focal or diffuse chronic inflammatory reaction, commenced in the common iliac arteries and decreased in severity and extent upward from the bifurcation of the aorta. It is suggested that the inflammatory process observed may have a part in precipitating the occlusion.

Alkaline Phosphatase in the White Cells in Leukaemia and Leukaemoid Reactions. B. J. Leonard, M. C. G. Israels and J. F. Wilkinson. Lancet 1:289-292 (Feb. 8) 1958 [London].

The authors describe a simple cytochemical technique for demonstrating alkaline phosphatase in leukocytes, which is a modification of Gomori's method. With this method alkaline phosphatase activity is shown as black granules in the cytoplasm of the neutrophil polymorphonuclear leukocytes. Lymphocytes, monocytes, plasma cells, eosinophils, and all blast cells show no activity, but they can be distinguished by their affinity for safranine. Phosphatase activity is expressed as absent, weak,

or strong, and an assessment is made by examining 400 consecutive neutrophil polymorphonuclear leukocytes. The percentage of cells with phosphatase activity was ascertained in 50 healthy persons, 50 patients with chronic myeloid leukemia, 50 patients with polycythemia vera, and 17 patients with leukemoid reactions. It was found that in chronic myeloid leukemia and acute neutrophil leukemia the alkaline phosphatase activity is reduced or absent.

In leukemoid reactions due to Hodgkin's disease, myelofibrosis, reticulosarcoma, carcinomatosis, polycythemia vera, hemolytic anemia, and tuberculosis, high levels of alkaline phosphatase were found in the leukocytes. The amount of alkaline phosphatase in the leukocytes appears to be regulated by the pituitary-adrenal axis. In complete remission in 2 cases of acute lymphatic leukemia that followed cortisone therapy, in spite of the apparent normality of the white blood cells, the phosphatase levels were high and remained so until the leukemia relapsed. The determination of alkaline phosphatase in the leukocytes is at present the best, and often the only, means of distinguishing between myeloid leukemia and leukemoid reactions involving the myeloid series of cells.

Malignant Testicular Tumours Following Mumps Orchitis. J. C. Giertsen. Acta path. et microbiol. scandinav. **42:**7-14 (No. 1) 1958 (In English) [Copenhagen].

In the case of 120 patients with malignant tumors of the testes, who were operated on at the University Hospital in Bergen, Norway, the surgical specimens were studied in the department of pathology, and in 5 of these patients a preceding mumps orchitis was revealed by the clinical records, representing an incidence of 4%. In addition, there was a 6th patient, a 51-year-old man, with a malignant tumor of the right testis after mumps orchitis, who had been operated on at another hospital and whose surgical specimen was referred to the author for pathological examination. These 6 patients were between the ages of 18 and 51 years at the time of the mumps orchitis, and the interval between the mumps orchitis and the clinical appearance of the tumor varied from 8 to 26 months, except for 1 patient in whom this interval was 20 years. The right testis or both testes were affected by the mumps orchitis; the tumor occurred in the right testis, except for the patient with the long interval between the mumps orchitis and the occurrence of the tumor, in whom the left testis was involved by the tumor. The type of tumor was embryonal carcinoma in 1 patient, seminoma in 3 patients, and chorioepithelioma in 2 patients.

The average interval of 19 months between mumps orchitis and the clinical appearance of the tumor in 5 of the 6 patients was strikingly short and compatible with a causal relationship between the 2 diseases. The facts that the tumor occurred in the same testis which was affected by the orchitis in 1 patient, that there was bilateral orchitis in 4 patients suggesting severe damage to the testes, and that in 1 patient the tumor occurred in the testis that was most severely damaged by the orchitis justify the discussion of a possible causal relationship between mumps orchitis and the occurrence of the tumor in these 5 patients. A direct relationship between the 2 diseases is less convincing only in the patient with the 20-year interval between the mumps orchitis and the occurrence of the tumor in the contralateral testis. It is well known that atrophic testes may become involved more frequently by a tumor than normal testes. A hormonal influence or disturbance is necessary for the experimental production of testicular tumors. Postorchitic atrophy with hormonal imbalance must, therefore, be regarded as a possible tumor-inducing factor, and it appears possible that mumps orchitis may have a tumor-inducing effect.

RADIOLOGY

Roentgen Manifestations of Torulosis (Cryptococcosis). J. N. Wolfe and G. Jacobson. Am. J. Roentgenol. **79:**216-227 (Feb.) 1957 [Springfield, Ill.].

Torula histolytica (Cryptococcus neoformans) is a fungus of world-wide distribution. It is usually a saprophyte, but as a pathogen it is more frequent than commonly supposed, as indicated by the cases of 21 patients seen at the Los Angeles County Hospital between 1945 and 1956. Seven of the 21 cases analyzed in this paper are described in detail. The epidemiology, mycology, and pathology of torulosis are reviewed briefly. There are no characteristic clinical features of the disease, and the diagnosis can be made only by recovery of the organism. The disease may be rapidly fatal or exist for periods of 12 to 15 years. Nine patients had pulmonary lesions which were nonspecific in appearance, ranging from segmental infiltrations to discrete mass lesions indistinguishable from primary or metastatic neoplasms. Both cavitation and mediastinal lymphadenopathy may be present. There were 3 patients with osseous lesions, consisting of a limited area of bone destruction with slight periosteal reaction. Six of the patients are living, 3 without evidence of disease. Pulmonary resection was performed in 2 of these 3 patients, and a bone lesion was curetted in the third.

Metastatic Lesions to the Large Intestine. R. Wigh and N. duV. Tapley. Radiology **70:**222-229 (Feb.) 1958 [Syracuse, N. Y.].

The authors report roentgenologic findings in 7 men and 23 women, between 32 and 85 years of age, with metastatic lesions affecting the colon. All the lesions were intra-abdominal or pelvic in origin, except for those in 2 patients who had lesions secondary to cancer of the breast and 1 patient who had a lesion secondary to squamous-cell carcinoma

of the leg. Two patients had had a primary malignant neoplasm of the large intestine, but the history and the surgical and pathological findings indicated that the newly discovered lesions were not additional primary carcinomas but were truly metastatic in type.

Eleven of the 30 patients had at least 2 defects shown by the roentgenograms, and 5 of these had 3 or more defects. Although primary carcinoma of the large intestine can be multicentric, this is not true of as high a percentage of patients as in the authors' study. There were 17 patients in whom the lesions were of annular type but in whom the typical shelving aspect of primary carcinoma was absent. Instead of presenting an abrupt transition between normal and affected intestinal wall, the extremities of the defects were tapered or conical. There was incomplete distensibility of the intestine, but contractility still remained. The roentgenoscopist frequently reported the presence of "spasm" or "irritability" in these areas. In areas of narrowing, both concentric and eccentric shadows were seen. Unilateral defects were noted in 11 patients. Marginal serrations in unilateral defects were noted in 6 patients and were interpreted as a neurogenic response to the presence of a contiguous mass in the mesentery.

The term "encapsulation" was coined for abnormalities consisting of trapping or enclosure of large portions of the colon in a sheath not normal to the part. In other patients, the contours of the intestine were of a lobulated character. There were only 2 patients with complete obstruction, but partial obstruction to the retrograde flow of the barium mixture was observed in 9 patients. Abnormal fixation in position of segments of the colon as a result of extrinsic pressure was observed in 15 patients; angular distortion or kinking proximally was found only occasionally. Assessments of the appearance of the mucosa were not easy. There were patients in whom the folds were obviously not destroyed at least in the tapered extremities of the deformity, and there were others with obvious abnormality of the mucosa, but the alterations were considered insufficient, in relation to the length of the area of involvement, to represent primary carcinoma. These roentgenologic features of patients in whom metastatic carcinoma affected the large intestine permit the conclusion that the roentgenologist can offer such a diagnosis with a high degree of confidence.

Roentgen Diagnosis of Pericardial Effusion: New Angiocardiographic Observations. I. Steinberg, H. V. von Gal and N. Finby. Am. J. Roentgenol. **79**:321-332 (Feb.) 1958 [Springfield, Ill.].

Thirty patients with pericardial effusion, studied by angiocardiography, form the basis of this report. They represent a selected series, because angiocardiography was utilized only in those patients in whom pericardial fluid was not clearly recognized and the differential diagnoses had to consider a dilated or an enlarged heart, a mediastinal tumor, or a pericardial tumor. In every instance, the characteristic feature of pericardial effusion, a heart surrounded by fluid, was demonstrated in frontal view. In the lateral projection, however, the pericardial fluid was always anterior, retrosternal, and infracardiac, causing backward displacement of the heart. It seems that small amounts of pericardial fluid first accumulate below the heart. The fluid extends anteriorly and then appears along the lateral borders of the heart with consequent "straightening." When massive pericardial effusions occur, the lateral pericardial recesses behave very much like water wings and extend laterally. These lateral pouches may fill asymmetrically, simulating pericardial or mediastinal masses. It is recommended that the anterior or infracardiac approach be used for pericardial paracentesis so as to avoid traversing the lung. Angiocardiography is recommended for diagnosis of pericardial effusions in problem cases. This method is preferred to diagnostic pericardial paracentesis, because enlarged and dilated hearts are easily lacerated. The increasing use of surgery for treatment and biopsy of the pericardium in pericardial effusions also makes preoperative diagnosis imperative.

BIOCHEMISTRY

Studies of One-Carbon Metabolism in Man. L. D. Goodwin and J. M. Kinney. J. Biol. Chem. **230**:487-496 (Jan.) 1958 [Baltimore].

In an attempt to compare the fate of preformed methyl groups with the fate of a compound chemically similar, and metabolically closely related, to 1-carbon intermediates, 2 men, 1 of whom was 70 years old with osteosarcoma and the other 69 years old with thyroid carcinoma, were given 200 μc of L-methionine-$C^{14}H_3$ (256 and 211 mg. of amino acid), and a third patient, a 41-year-old man with lipomatosis, was given 200 μc of sodium formate-C^{14} (13 mg.). The 3 patients were hospitalized in the metabolic ward of the James Ewing Hospital unit of Memorial Center in New York; they were in good general condition, ambulatory, and were receiving the regular hospital diet. After ingestion of the labeled compounds, the isotope appeared rapidly in respiratory carbon dioxide and urea, in uric acid and creatinine, and in the amino acids of plasma protein. Amino acids were isolated by ion exchange chromatography from total protein samples, and creatinine was obtained from serial urines. Of the 17 amino acids isolated, methionine, serine, cystine, alanine, glutamic and aspartic acids, glycine, and arginine displayed significant radioactivity. The interrelations represented by these and other compounds examined, involving 1-carbon and amino acid metabolism, have been discussed; in general, the pathways indicated

in man are consistent with those already established in mammalian studies. Evidence is presented for the occurrence of methyl synthesis in man. The 1-carbon intermediates derived from methionine and formate are readily incorporated into serine. The labeling of creatinine provides further evidence of transmethylation as a physiological process in man.

Respiration of Human Skin: Normal Values, Pathological Changes and Effect of Certain Agents on Oxygen Uptake. E. Leibsohn, B. Appel, W. C. Ullrick and M. J. Tye. J. Invest. Dermat. **30**:1-8 (Jan.) 1958 [Baltimore].

The aim of the studies described was to establish the mean energy requirements of human skin, indirectly, as measured by the oxygen absorption. The requirements of the epidermis were differentiated from those of the whole skin, and these values were related to the energy requirements of other organs of the body and of the body as a whole. Biopsy specimens of human skin, taken without the patients being under anesthesia, from about 7.5 cm. below the shoulder, on the lateral aspect of the arm of individuals of varying age, sex, and race, were used in the study for normal values. Pathological skin specimens were obtained from patients at the site of active lesions. Warburg's technique was used for the respiratory measurements. The studies involved mechanical separation of the epidermis from most of the dermis and calculating the respiration of the pure epidermis. In 22 biopsy specimens of normal skin, the mean Qo_2 (rate of oxygen consumption in microliters per hour per milligram of tissue) for the dermis was 0.49 ± 0.12. The calculated Qo_2 in 16 specimens for the pure epidermis was 4.53 ± 1.39. The epidermal-dermal difference was highly significant statistically. It was estimated that the skin requires 7% of the normal, resting, total body oxygen consumption: 4% for the epidermis, 3% for the dermis. In terms of heat production this represents 2.04 and 2.64 calories per hour for the dermis and the epidermis, respectively, or 4.68 calories per hour for the skin as a whole.

The data obtained show that a large degree of variation exists among the individual values for dermal and epidermal respiratory rates and is evidenced in the rather large standard errors. This in itself may prove to be of interest. Part of the large variability in the data is probably due to the fact that human material is much more heterogenous than is animal tissue. The age, sex, race, etc., of the individuals from whom the biopsy specimens were taken may contribute to the scatter in the results. In spite of the large variation in the individual results, the respiration of epidermis is higher statistically than the respiration of dermis. This is understandable; one would expect the epidermis to be more active metabolically than the dermis because of its functions of cell division and growth. No general statement can be made on the pathological skin specimens, because the studies are still in the preliminary stage.

Utilization by the Human Organism of Peptides of Bovine Blood Protein Hydrolyzate. K. Raczyńska-Bojanowska and I. Chmielewska. Bull. Acad. polon. Sc. **6**:1-6 (No. 1) 1958 (In English) [Warsaw, Poland].

Fifteen patients who had been operated on for gastric ulcers and 3 healthy persons were studied in an attempt to ascertain which bovine blood protein hydrolyzate, the one with a large or the one with a small peptide content, when intravenously administered, is more valuable for the human organism. Preparations of varying peptide content were obtained as a result of different conditions of proteolysis. The peptide amino nitrogen content varied from 15 to 41% of total amino nitrogen, i. e., from 0.8 to 2.3 Gm. of amino nitrogen bound in peptide bonds per 1,000 cc. of 7% hydrolyzate. Seven of the 15 patients operated on for gastric ulcer received the usual light hospital diet and 3,500 to 10,500 cc. of the hydrolyzate administered intravenously after the operation; the other 8 patients did not receive the hydrolyzate after the operation. The 3 healthy persons received a full caloric nonnitrogen carbohydrate and fat diet and, in addition, 1 liter of the hydrolyzate administered intravenously.

Determinations of amino nitrogen in free and bound amino acids excreted in the urine by the patients with gastric ulcers before and after the operation showed that the operation alone increased the excretion of amino nitrogen of free and bound amino acids from 1½ to 6 times, the increase being greater in the case of bound amino acids. The administration of the hydrolyzate increased further the amount of both free and bound excreted amino acids. There was, however, neither proportionality nor positive relationship between the amount of bound amino acids given in the hydrolyzate and those excreted in the urine by the patients operated on. The amount of excreted amino nitrogen of bound amino acids is more or less the same and depends neither on the amount administered nor on the type of the hydrolyzate. Thus, a great part of peptides given in the hydrolyzate of high-peptide content are metabolized by the human organism. It follows then that the hydrolyzate of high-peptide content is at least as valuable as the hydrolyzate of low-peptide content. The results obtained in the healthy persons were in agreement with those obtained in the patients in proving that a considerable part of the hydrolyzate peptides is metabolized by the human organism.

BOOK REVIEWS

Office Gastroenterology. By Albert F. R. Andresen, M.D., Attending Physician, Long Island College Hospital, Brooklyn. Cloth. $14. Pp. 707, with 110 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W. C. 2, England, 1958.

This monograph, based on the personal experience of the author, should be of primary interest and value to the general practitioner and internist. Although the material is well organized and covers the specialty, depth is occasionally sacrificed for brevity and perspective is occasionally distorted in an attempt to present personal views with sincerity and integrity. An example is the author's emphasis that allergy is largely responsible for the exceedingly variable gastrointestinal symptoms, so often more conventionally attributed to functional gastrointestinal disorders. Another example is the author's belief in the value of the eradication of foci of infection in the prevention and relief of peptic ulcers. The first section consists of a plan of attack on gastrointestinal disease. This deals with the fundamentals of history taking, physical examination, and general physiology as a springboard for treatment. Other sections deal with the various diseases of the gastrointestinal tract, their symptoms, diagnosis, and treatment. Especially in this section, the scarcity of good illustrations and the singular approach to therapy are most obvious. The interdependence of gastrointestinal symptoms with those of the cardiorespiratory and genitourinary systems is included. The treatment of diseases of the hepatic and biliary systems is adequate. The material is up to date and timely and includes words of caution on evaluating anticholinergics, corticosteroids, tranquilizers, and antibiotics. The author has presented physicians of all interests with a highly readable and inclusive book on gastroenterology. Although his work has confessed limitations, it represents the experience of one who is highly respected in this field.

The Medical World of the Eighteenth Century. By Lester S. King, M.D. Cloth. $5.75. Pp. 346, with illustrations. University of Chicago Press, 5750 Ellis Ave., Chicago 37; Cambridge University Press, Bentley House, 200 Euston Rd., London, N. W. 1, England; University of Toronto Press, Toronto 5, Canada, 1958.

A book on any phase of the history of medicine is likely to be doubly interesting, because there is intrinsic fascination in the doings of humanity in the past and because the reader might thereby be enabled to spare himself a repetition of old mistakes. Focused on the medicine of the 1700's, this book gives some startling descriptions of life in an age when physicians had no thermometers, their watches had no second hands, surgeons had no anesthetics, and their patients had only the most rudimentary ideas of cleanliness. It traces the slow progress of medical science in that century, through innumerable contributions, large and small, but especially those of Hermann Boerhaave. It also traces the development of medical ethics and medical organizations through innumerable conflicts of specialty with specialty and of one profession with another. The text is made readable by the author's clear, unaffected style and by his choice of a wealth of vivid detail. The work is carefully documented, annotated, and indexed. The printing is flawless and the make-up attractive. This book is recommended to everyone who is interested in the continued progress of medicine both as a science and as a profession.

Digitalis. Compiled and edited by E. Grey Diamond, M.D., Professor and Chairman, Department of Medicine, University of Kansas Medical Center, Kansas City. Cloth. $7. Pp. 255, with illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., Blackwell Scientific Publications, Ltd., 24-25 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto 2B, Canada, 1957.

This book consists of a collection of papers presented at the University of Kansas Medical School during a two-day symposium in February, 1956. Several additional papers on the history and metabolic fate of digitalis are also included. Since digitalis is currently the most frequently used, and probably misused, therapeutic agent for the relief of cardiac decompensation, the editor should be commended for making a review of this nature on this drug available to the medical profession. The value of this volume is somewhat lessened by the uneven quality of some of the papers. For example, the chapter on the pharmacological basis of action pales by comparison with the more thorough presentation of material in the following sections on the physiological actions, the metabolic fate, and the therapeutic applications of digitalis and its glucosides. The absence of a bibliography in several papers is unfortunate. There is a particularly interesting chapter on the auricular arrhythmias caused by digitalis overdosage. It is disappointing that a discussion of the treatment of the auricular arrhythmias is not included. The book is well indexed and typographically and otherwise

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pleasantly readable. Perhaps the most stimulating portion of this volume is the panel discussion. The editor, acting as moderator, encouraged a clarification of certain controversial statements made by some of the contributors. Here the greater therapeutic range for gitalin, advocated by Batterman, and the safety of the acetyl strophanthidin test by Lown were placed in a more proper perspective. Although this book is not without faults, it affords an excellent review of the subject, representing an extensive assemblage of information and experience with digitalis. It should be a useful and provocative source book for the practitioner and the student interested in the pharmacology and clinical use of digitalis.

Human Blood Coagulation and Its Disorders. By Rosemary Biggs, B.Sc., Ph.D., M.D., Graduate Assistant in Department of Pathology, Radcliffe Infirmary, Oxford, and R. G. Macfarlane, M.A., M.D., F.R.S., Clinical Pathologist to Radcliffe Infirmary. Second edition. Cloth. $8.50. Pp. 476, with 53 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, 24-25 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto 2B, Canada, 1957.

This new edition of a well-known book should be of great value to the student of coagulation, featuring as it does the coagulation disorders. One hundred ninety-four pages are taken up with the theories of blood coagulation and various blood clotting factors. There is an excellent section on hypoprothrombinemia, a relatively small one on hemophilia, and a good section on fibrinogen deficiency. The section dealing with thrombosis and anticoagulant therapy is outstanding, but the clinical sections are relatively poor and contain little information. Thus, the general subject of hemostasis and the hemorrhagic disorders is not as well covered as it might be. This is perhaps due to the particular bias of the authors, who have been among the foremost students of blood coagulation but whose work with clinical material has not been correspondingly as great.

Clues to Suicide. Edited by Edwin S. Shneidman, Ph.D., and Norman L. Farberow, Ph.D. Foreword by Karl A. Menninger, M.D. From Veterans Administration Neuropsychiatric Hospital and Veterans Administration Mental Hygiene Clinic, Los Angeles. Investigation supported in part by research grant, M-1074, from National Institute of Mental Health, of National Institutes of Health, U. S. Public Health Service. Cloth. $5.50. Pp. 227. Blakiston Division, McGraw-Hill Book Company, Inc., 330 W. 42nd St., New York 36; 95 Farringdon St., London, E. C. 4, England; 253 Spadina Rd., Toronto 4, Canada, 1957.

These 18 chapters by as many authors cover various aspects of suicide. The editors demonstrate that, although many persons who never attempt suicide imply that they are considering it, few people commit suicide without giving clues that herald the actual event. If these communications are heeded and efforts made to interrupt the otherwise natural course of events, many suicides can be prevented. Suicide ranks among the first 10 in the list of causes of death in the United States, and, as such, it is of great importance to the physician. Since suicide affects society in many ways, the contributors to this volume are concerned with the cultural, sociological, legal, medical, and psychological aspects of the problem. This book, therefore, is a searching survey, not a definitive evaluation, and its value lies in this fact. Part 1, in addition to describing an experimental approach to the psychological aspects of suicide, deals with theoretical considerations. There are five chapters on the meaning of suicide as seen from as many viewpoints. Three chapters broaden the general discussion with their focus on the religious, legal, and sociological implications of this problem. The nine chapters in part 2 illustrate clinical aspects of suicide, including brief descriptions of the psychotherapy of suicidal patients and some pertinent suggestions for suicide prevention. The papers are slanted more to the psychiatrist than to the general practitioner.

Psychiatry and the Criminal: A Guide to Psychiatric Examinations for the Criminal Courts. By John M. Macdonald, M.D., Assistant Professor of Psychiatry, University of Colorado School of Medicine, Denver. Cloth. $5.50. Pp. 227. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, Ltd., 24-25 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto 2B, Canada, 1958.

A guide in the difficult area of forensic psychiatry is here presented briefly and concisely. That it will achieve one of the stated aims of stimulating interest in entering the field is doubtful, but the practical experience represented is valuable. Following a brief treatment of the sociological, biological, and psychological factors of criminal behavior, the problem of responsibility is considered. The difficulties in avoiding the right-wrong, irresistible impulse test of responsibility is demonstrated, together with the attempts to develop sounder concepts, based on a psychiatric orientation. The recognition of the influence of unconscious on conscious processes and that a reverse influence also operates forms a sound viewpoint in determining responsibility and management of the criminal. The special problems involved in the examination for court purposes and some of the more common reactions, such as the Ganser syndrome and simulated insanity, are outlined. It is pointed out that narcoanalysis is not an infallible device and involves special ethical considerations. Amnesia, epilepsy, sex offenses, and alcoholism are also discussed. Useful information of a practical sort is pointed out in the sections on preparation of reports and appearance on the witness stand. This useful presentation of the neglected field of the psychiatric examination and management of the criminal stresses rehabilitation rather than revenge.

QUESTIONS AND ANSWERS

COMPLICATION DUE TO STEROID THERAPY

To the Editor:—*A 60-year-old woman has had rheumatoid arthritis for the past three years. She was maintained first on therapy with cortisone acetate for two years and then with 5 to 10 mg. of prednisone daily for about one year. This was the only therapy that would give her relief. After the latter period of therapy, a perforated duodenal ulcer was repaired surgically. Since that time, the patient has been bedridden but has not received further steroid therapy. Her joints, especially her fingers, are swollen and painful, but she does not have marked deformity of the joints or extremities. Would it be advisable to again attempt steroid treatment for short periods? It has been six months since the operation. Would ACTH be contraindicated? The patient gets no relief from any other therapy and believes that she could walk again if she received the steroids.*

J. L. Gardner, M.D., Hendersonville, N. C.

Answer.—This difficult clinical problem is frequently encountered in rheumatic disease centers. The patient had one of the more serious complications of corticosteroid therapy for rheumatoid arthritis, with a fortunate termination. Most investigators and experienced clinicians would advise that, in a patient who recently has had an ulcer during corticosteroid administration, it would be better not to give corticosteroids. However, under certain circumstances the decision is made to readminister these drugs even though risks may be greater than average. All nonsteroid therapy that can reasonably be expected to relieve the patient should be thoroughly tried. If gold therapy has not been adequately used, it would be wise to attempt to suppress the rheumatoid activity with this form of therapy. If one or two large joints are persistently affected, trial of intra-articular corticosteroid might be found adequate so that systemic steroids may not be needed. If gold cannot be tolerated or if it and other treatment are ineffective, a reconsideration of corticosteroid therapy is justified. The patient and all concerned should be fully aware of the circumstances and factors involved. If, after careful consideration, it is decided that the potential benefit outweighs the risk of steroid therapy and if the patient fully appreciates the hazards involved, cautious trial of the treatment may be decided on. Corticotropin needs to be considered in the same way as corticosteroid. There is no difference between the action of these hormones in this set of circumstances. That the ulcer has been healed for six months or longer is no assurance that a new ulcer or reactivation will not develop. Because a recent peptic ulcer has occurred, even though it is healed, there is greater risk of peptic ulcer complicating readministration of steroids. Although there is some suggestion that the new synthetic corticosteroids may have less ulcerogenic properties, ulcers have developed in patients receiving all of the currently commercially available steroids, including triamcinolone diacetate and methylprednisolone.

If it is decided to readminister corticosteroid to this patient, an upper gastrointestinal series and tests for occult blood in the feces should be made before commencing this treatment. Had partial gastric resection been done after perforation of the previous ulcer, there would be less risk of ulceration with readministration of steroids. One of the new synthetic corticosteroids (triamcinolone or methylprednisolone), in a dosage not exceeding 8 mg. daily, should be adequate for the desired partial suppression. Large doses of antacids should be given during steroid administration. Frequent blood cell counts and tests for blood in the feces are advisable, and a gastrointestinal series should be done every three months while the patient is receiving this treatment. If the steroid therapy does not give good results, it should be stopped.

FLARING OF XIPHOID AND COSTAL CARTILAGES DURING PREGNANCY

To the Editor:—*A young woman noted during her first pregnancy a flaring of xiphoid and costal cartilages of the 9th and 10th ribs on the left side of the thoracic cage; this has persisted for eight months after delivery. Would some kind of binding help restore cosmetic appearance?*

M.D., Virginia.

Answer.—It is not felt that this flaring is a result of the pregnancy. If the woman is quite young, there is, of course, the possibility that there might have been some vitamin deficiency which would predispose to the flaring of her ribs. It is rather doubtful that any sort of binder or appliance would help to correct the deformity, though it might be worth trying. A tight brassiere, with a broad band on the lower portion, might be sufficient to do some good.

The answers here published have been prepared by competent authorities. They do not, however, represent the opinions of any medical or other organization unless specifically so stated in the reply. Anonymous communications cannot be answered. Every letter must contain the writer's name and address, but these will be omitted on request.

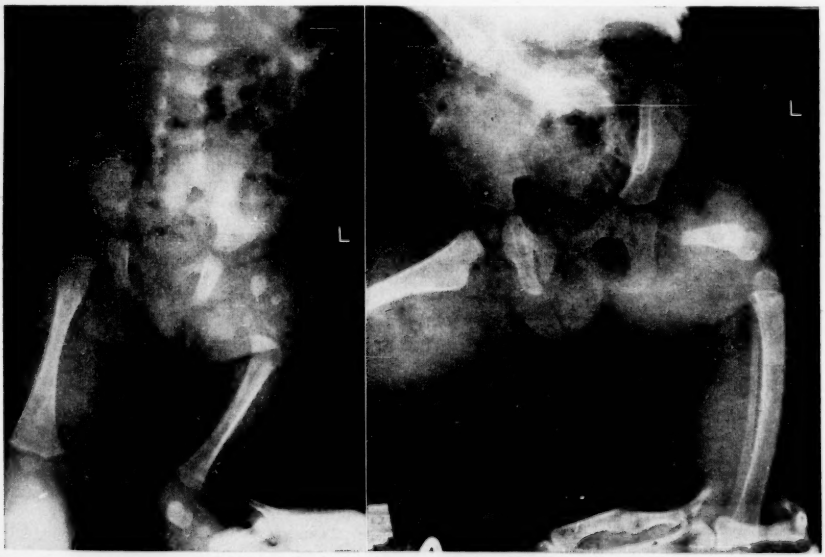
CONGENITAL ABSENCE OF FEMUR

To the Editor:—*A 15-month-old girl with congenital absence of the proximal two-thirds of the left femur has been brought to the United States from South America. X-ray films (see figure) show no ossification centers of the femora capitis and trocanters. Comparison with films taken eight months earlier revealed progress in the growth of the distal part of the femur. An orthopedic center in the United States advised amputation of girl's left foot and application of a prosthesis. Is there any possibility that the proximal ossification centers of the femur might appear spontaneously in the future? Might use of growth hormone, if available in pure form, induce the appearance of those centers? Would autografts taken from carpal bones or the fibula be useful?*

M.D., New York.

Answer.—The answer to all three questions is no. The advice that the parents have received regarding the amputation of the foot and the application of a prosthesis is sound. The question is only when this had best be done. There is no harm in waiting, and, in the interim, an ischial weight-bearing brace with adjustable length could be made and she could be trained in its use.

Answer.—The answer to the first question is no. One might state further that, if the proximal ossification centers of the femur did appear, there is so much soft tissue shortening that it would not do any good. There is no reason to expect that a growth hormone might do other than induce growth where cells of a certain growth potential are present. If those cells are not present, the growth hormone cannot produce them. Autografts from the carpal bones or the fibula, even including the epiphysis, are theoretically and perhaps actually feasible at the present time, but the soft tissue shortening in the leg is such that no useful purpose could be served even if the grafts were successful. The following treatment, however, has been successful. If arthrodesis of the remaining portion of the femur and the innominate bone on the same side is done in the proper position, a satisfactory range of flexion, extension, abduction, and adduction can be obtained. Further, a 180-degree rotational osteotomy of the tibia will bring the foot into such a position that the ankle joint can act as a knee joint and the action of the gastrocnemius–soleus muscle groups on the oscalcis can be made to extend the knee joint of a prosthesis, which can then be satisfactorily fitted without amputation and without discarding any useful structure.



X-ray films showing absence of proximal two-thirds of left femur, with normal right femur. *Left*, film taken at 3 months of age. *Right*, film taken at 15 months, with evidence of growth of distal part of the femur.

STATIC EDEMA

To the Editor:—*A 41-year-old man has suddenly developed pitting edema of the feet, ankles, and calves, which recedes almost completely over night. He walks 8-15 miles per day, and he eats a high protein diet. Blood protein level, complete blood cell counts, and findings in repeat urinalyses are all normal. There is nocturia one to two times regularly. Blood urea nitrogen levels were recently 23.1 and 25 mg. per 100 cc., and the phenolsulfonphthalein excretion was 40% the first half hour, 55% in one hour, and 63% in two hours. Protein-bound iodine level was 2.6 mcg. per 100 cc., and the serum cholesterol level was 252 mg. per 100 cc. He eats daily about 1 lb. of raw cabbage and 1 lb. of raw carrots. Is it possible that this intake of these vegetables could play a part in the edema?*

William R. Moses, M.D., Falls Church, Va.

Answer.—Edema of cardiac and renal failure can apparently be excluded in this person. In addition, there is no evidence that the edema is secondary to hypoproteinemia and hyperlipemia. The daily ingestion of unsalted large quantities of raw cabbage and raw carrots does not appear to have a causal relation to the edema. However, it may be that this individual is dipping these vegetables in sodium chloride while eating them. These raw vegetables have a relatively low content of chloride and sodium, but it is of interest that both contain a considerable amount of potassium, which has a diuretic action, in contrast to the water-retaining effect of chloride and sodium. Further, raw carrots contain a large quantity of vitamin A. This consultant, therefore, concludes that this man's edema is most likely static in type. It may be due to obstruction of venous or lymph vessels of the legs, and this possibility should be excluded. There are rare instances of this type of edema in which it is difficult to assign the exact cause.

Answer.—The low protein-bound iodine and elevated serum cholesterol levels, coupled with the other findings, suggest a hypothyroid state, with perhaps some cardiac involvement. In view of the very high protein diet and the other indications of adequate nutrient intake, it seems improbable that the findings are due to a dietary deficiency of protein. The informant does not indicate how long the patient has consumed the quantity of 1 lb. of raw cabbage per day. Nevertheless, it seems possible that, if this level of consumption has been continuous over a prolonged period, the patient may have diet-induced hypothyroidism, since it is known that cabbage contains goitrogenic substance. It has long been known that large quantities of cabbage fed to rabbits will produce goiter. Both thiocyanate and the goitrogen, L-5-vinyl-2-thiooxazolidone, have been incriminated. The latter occurs in a considerable number of members of the genus Brassica. Recent evidence from Australia has demonstrated that dietary goitrogens can, in fact, alter iodine metabolism in man. Accordingly, it would seem logical to interdict the large quantities of cabbage in the diet of this patient and to obtain further evidence concerning the thyroid function and changes in this during the weeks after omission of cabbage from the diet.

This consultant has been unable to find any reference to an effect of large amounts of raw carrots which might bear on this problem. During periods of starvation it is true that individuals subsisting to a large extent on root crops (turnips, carrots, and tubers) may develop hypoproteinemic edema. This would certainly not seem to apply in the present instance. There exist some indecisive claims in the literature concerning the goitrogenic influence of avitaminosis from deficiency of vitamin A, but, again, the quantity of vitamin A (or its precursor, carotene) in this patient's diet is clearly abundant. The one diet-induced nondeficiency edema which has been widely studied is "epidemic dropsy," which has been reported in India. This syndrome is characterized clinically by cardiovascular, cutaneous, and alimentary manifestations which, superficially, resemble beriberi. Onset may be gradual or sudden, and diarrhea is present and continuous. Edema of the feet and legs occurs, and the skin exhibits hyperemia with vascular mottlings and, sometimes, petechia. Evidence now seems convincing that the toxin concerned is from contamination of mustard oil by argemone oil (from the prickly poppy, Argemone mexicana). There is no reason to suspect this agent in the present case.

CONTRAINDICATIONS TO CIRCUMCISION

To the Editor:—*Would any of the following conditions be considered contraindications to circumcision, done at the age of 8 days? These conditions include (1) prematurity, i. e., about 4 lb. (1.8 kg.); (2) neonatal complication, such as cyanosis, infection, or excessive weight loss (if the infant has recovered by time of circumcision); (3) physiologic jaundice; and (4) erythroblastosis fetalis and other hematological conditions. Would vitamin K protect against bleeding, since there is some hepatic effect in all the above conditions? In general, is there any need to postpone the procedure if the neonatal course is abnormal?*

Milton R. Aisenson, M.D., Flushing, N. Y.

Answer.—No hard and fast generalizations can be made in answer to these questions, because circumcision has probably been safely carried out in each of the listed conditions. However, conservative management should take the following information into consideration: 1. Coagulation defects (low prothrombin content and decreased plasma thromboplastin component and proconvertin) are found

in both the full-term and the premature infant during the neonatal period. These defects potentially lead to excessive bleeding (Aballi and others: *A.M.A. J. Dis. Child.* **94**:589, 1957). Whereas vitamin K controls these deficiencies in the full-term infant, it is less effective in the premature child. Circumcision should therefore be deferred in the latter for a period of about three to four weeks. 2. It is difficult to conceive that within a period of a week an infant should have recovered completely from the complications mentioned. Here, too, circumcision should be deferred. 3. Physiologic jaundice is no contraindication to circumcision. 4. The patient with erythroblastosis fetalis presumably is still under surveillance, and elective operative procedures should be postponed until the hemolytic process has subsided. In hemorrhagic disease of the newborn, congenital thrombocytopenic purpura, and those coagulation disorders occurring in the newborn infant with a suspicious family history of bleeding (classical hemophilia and other subtypes of this disease), operative procedures should be avoided until the particular defect has been investigated. With the exception of hemorrhagic disease of the newborn, vitamin K is ineffective in improving the bleeding disorders mentioned. In general, it is advisable to postpone circumcision within the first week of life in situations where an underlying bleeding disorder may be operative or where the neonatal course is complicated by serious illness. Unfortunately, there are no simple laboratory procedures that serve as a screening test for possible clinical bleeding.

MALIGNANT SYNOVIOMA

To the Editor:—*In May, 1949, a high amputation of the right thigh was done on a 21-year-old woman for malignant synovioma of the right knee of two years' duration. In September, 1955, biopsies were performed on both breasts and six tumors were removed. The pathologist reported metastatic synovial carcinoma. Roentgenograms in July, 1956, revealed a mass in the right hilar region. In April, 1957, two areas in the right hilar region were found, and these have increased slightly. On Feb. 3, 1958, the patient was given an initial dose of 10 mg. of nitrogen mustard intravenously and daily thereafter for a total of 40 mg. She has been comparatively symptom free, taking care of a house and two active children. Considering the abnormally long survival with this highly malignant tumor, is there any suggestion as to additional therapy? Because of the poor prognosis, no therapy was given prior to the nitrogen mustard other than surgery.*

Albert I. Clark, M.D., Shreveport, La.

Answer.—According to Ackerman and del Regato (Cancer, ed. 2, St. Louis, C. V. Mosby Company, 1954), patients with undifferentiated fibrosarcomas, liposarcomas, leiomyosarcomas, angiosarcomas, rhabdomyosarcomas, and synovial sarcomas, as a group, have a poor prognosis, no matter what the treatment, and only rarely can a patient be saved by initial radical surgery. In the case of synovial sarcoma (Willis, R. A.: Pathology of Tumours, St. Louis, C. V. Mosby Company, 1948), the lungs are the main site of metastases, which may appear several years after removal of the primary growth. It seems reasonable to assume that the pulmonary nodules in this patient are metastatic. It is not clear why chemotherapy was used in February, 1958, or whether it had any objective effect on the pulmonary lesions or on the clinical condition of the patient. If either subjective or objective improvement was noted, maintenance chemotherapy would certainly deserve a trial, especially in view of the patient's youth and the ultimate gravity of her prognosis. Either sterile mechlorethamine hydrochloride or triethylene thiophosphoramide (ThioTEPA) could be given. The latter agent has the advantage of greater ease of administration and absence of clinical toxicity. Hematological depression occurs with either drug, but it can be controlled, is reversible, and is not too great a penalty for control of a lethal disease. A recommended dosage schedule would be 0.1 mg. per kilogram of body weight of mechlorethamine or 20 mg. of triethylene thiophosphoramide intravenously every 10 days. A white blood cell count should be obtained prior to the injection, and, if below 3,000 per cubic millimeter, the dose should be reduced. If it is below 2,000 per cubic millimeter, the dose should be omitted. An intramuscular injection of a long-acting adrenocorticotropic hormone (40 units) given at the time of chemotherapy is good adjuvant therapy in such cases.

CAUSE OF JAUNDICE

To the Editor:—*Please give information on the possible causes of jaundice in the following case. A 50-year-old man was operated on for obstructive jaundice. The postoperative diagnosis was chronic pancreatitis, based on the finding of a hard, enlarged, nodular head of the pancreas. The biliary duct system was normal in all respects, except for some adhesions about the gallbladder. Probes from 2 to 10 mm. in diameter were easily passed through the ampulla of Vater. The liver, except for a rounded edge, was apparently normal. It is not believed that the jaundice was caused by obstruction in the pancreatic portion of the common bile duct. Could hepatitis be a cause of the jaundice in this case? Is hepatitis an accompanying feature in pancreatitis?*

M.D., New York.

Answer.—If the common bile duct in this patient was not obstructed, the jaundice would have to be explained on the basis either of some form of hepatitis or intrahepatic malignancy, or of a hemolysis. Cirrhosis was apparently absent on gross examina-

tion of the liver. Liver function tests in all of these conditions would be helpful in distinguishing between them and common bile duct obstruction. A drug-induced jaundice, such as that from chlorpromazine, however, can produce results of liver function tests similar to those observed in obstruction.

CHRONIC AMEBIASIS

To the Editor:—*A 35-year-old man has chronic amebiasis with ulcers of the colon. He has complained of recurrent diarrhea with blood and mucus in the stools for more than four years, with severe pain in right upper abdominal quadrant. Since the onset of the disease, full courses of therapy with emetine hydrochloride, chiniofon, diiodohydroxyquin, carbarsone, Comoform (biallylamicol hydrochloride), and antibiotics, mainly oxytetracycline and chlortetracycline alone or in combination, have been given. After each treatment, the patient improved but always relapsed. Recently, the relapses have become more frequent and refractory to treatment with the above drugs. The patient's general condition is getting worse. Since January, 1958, he has taken 3 capsules of oxytetracycline and 1 Gm. of carbarsone daily, but the abdominal pain has not been relieved and now radiates to the shoulder and back. Fluoroscopy and roentgenograms revealed multiple ulcers of the hepatic flexure of the colon. At present, no amebas are found in the stools. The liver is palpable one fingerbreadth below the right costal margin. Results of liver function tests are normal. The patient has no fever but is emaciated. Are there any drugs that will completely cure amebiasis? Can amebic ulcers of the colon be cured by repeated use of amebicides? Would resection of the ulcerated position of the colon help this patient?*

Wan Sheng Chhuang, M.D., Formosa, China.

Answer.—The case related suggests repeated reinfections by the Entamoeba histolytica, possibly with the development of a superimposed ulcerative colitis of a variety caused by some other infectious organism. This statement is made because the physician making the inquiry states that the patient has had "full courses" of treatment with the accepted amebicides. It is inadvisable, however, to give such large doses of carbarsone over an extended period of time. The proper combination of emetine hydrochloride, carbarsone, and one of the oxyquinoline drugs, given in suitable amounts properly timed, almost invariably eradicates the amebas from the intestine. The problem of reinfection, however, is the important one. Amebic ulcers usually heal after eradication of the ameba. If such a condition is due to amebiasis, resection should almost never be considered. It is important to determine the nature of the present ulcerative condition of this patient's intestine.

KERNICTERUS

To the Editor:—*A patient, aged 24, is presently three and one-half months pregnant with her fifth pregnancy. She is Rh-positive; her blood type is "O"; and serologic studies were negative. When she was 17 years of age, her spleen was removed because of severe spherocytosis with jaundice and secondary anemia (familial hemolytic jaundice), and later a stone was removed from her common bile duct, which was producing biliary colic. Her gallbladder was normal. Her second pregnancy was uneventful except that the baby developed severe icterus neonatorum, which resulted in a cerebral hemorrhage and spasticity. Her third pregnancy was uneventful, with the exception that the infant developed moderate jaundice. The fourth pregnancy was uneventful, and the infant seemed normal at delivery; however, by the sixth day the child developed a deepening jaundice, went into opisthotonos, and died. The mother had had the usual prenatal medication to prevent anemia and to supply adequate calcium and vitamins. Prior to delivery, she received vitamin K for 10 days, and after delivery both infant and mother were given this by injection. Subcutaneously given fluids were supplied the infant, but to no avail. Please give advice and counsel as to what to do for this patient. Can splenectomy be performed in a newborn infant?*

M.D., Wyoming.

Answer.—This query presents many problems. Hereditary spherocytosis is seldom manifested in the newborn period, and kernicterus has been described in only one case, so that it is unlikely that these children have this disease at birth. Other conditions must be strongly considered in this case. The most likely is erythroblastosis, despite the fact that the mother is Rh-positive. ABO and other less common blood groups may lead to severe erythroblastosis. The other possibility is that of vitamin K intoxication. Large doses of vitamin K have been known to cause kernicterus. During this pregnancy, the mother's blood should be investigated for sensitization to A, B, and other rare blood group antigens. The father and the living children should also have their blood examined. In this manner, a fair guess may be made as to the possibility of the next child being affected with erythroblastosis. Vitamin K is probably not necessary, but, if given, it should only be given in 1-mg. doses once daily for three days. Exchange transfusion is the treatment of choice after the child is delivered. It should be performed as soon as a diagnosis of sensitization is made, either immediately after delivery or at the onset of jaundice from whatever cause. Exchange transfusion should be repeated within 24 hours if the bilirubin level remains elevated. A splenectomy would hardly be of any value, as the immediate danger is that of kernicterus and usually can be prevented by exchange transfusion.

PAINFUL EDEMA

To the Editor:—*A 31-year-old executive has had a hard, painful edema of the back of the left hand and the left wrist for four years. There has been no injury, and his history is entirely negative. The pain is practically continuous but varies in severity, and has a tendency to be most pronounced in the early morning. There is slight muscular atrophy of the affected extremity and a moderate limitation of the movements of the fingers and hand. Treatment, including that with hydrocortisone, x-ray, plaster immobilization, physiotherapy, and salycilates, has been tried without success. Please suggest a diagnosis and recommend treatment.* *M.D., Belgium.*

Answer.—The diagnosis is dermatomyositis. The localization is unusual, but the combination of dermatitis and myositis, in an adult, with changes in the skin, muscle, blood vessels, and subcutaneous tissues of an inflammatory nature, could only indicate this relatively rare disease. There is no specific therapy. The treatments listed are the usual ones. If these have failed to relieve the condition, one can only hope for a localization of the disease to its present site and for the appearance of a remission, which not infrequently occurs and may be prolonged and even complete.

Answer.—From the description of the hand, the disease would seem to be in the nature of a localized type of lymphatic stasis. Since it has been present for four years, a biopsy of the most involved area would be indicated. For treatment, a brachial plexus block on the left side might be attempted. There is no notation that this patient has had adequate support to this hand in the nature of either mechanic's waste or fluffs followed by pressure from an elastic type of woven bandage.

ISOLATION OF PARAKEETS TO PREVENT TRANSMISSION OF PSITTACOSIS

To the Editor:—*In the Queries and Minor Notes section of* The Journal, *Sept. 7, 1957, page 113, the answer to the question on psittacosis stated that the dosage of tetracycline compound to render birds noninfectious should be interrupted and not less than 30 mg. over a period of 15 days. What is the maximum dose that may be given orally to a parakeet daily? How should the dosage be scheduled? Should it be administered in the feed or by an eyedropper? Does the recommended dosage cause diarrhea or other symptoms of toxicity? Can parents be assured the treatment is effective in eliminating carriers in 100% of the cases, or is it best to advise them not to keep psittacine birds?*

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The above comment was referred to the consultant who answered the original question and his reply follows.—Ed.

To the Editor:—*Parakeets fed a mash containing tetracycline compounds consumed 20 mg. of the drug a day. This dosage caused anorexia and diarrhea. If this heavy dosage was continued for 5 to 10 days, some of the parakeets died and yeasts were isolated from the intestines. The daily oral intake of tetracycline compounds should not exceed 10 mg. The drug is administered either in a specially prepared medicated millet seed (developed at the University of California Medical Center, San Francisco) or in the drinking water. The hulled millet seed was impregnated with chlortetracycline at a level of 0.5 mg. of drug per gram of feed and administered for three consecutive days, followed by two days of feeding with regular seed, until the completion of five treatment periods (15 days of medication). The special feed may become available commercially in the near future. Drinking water is medicated at the level of 0.8 mg. of tetracycline per milliliter and is offered to the bird continuously for two to three weeks. The therapeutic results with the medicated water were similar to those with the feed, but the method is not considered the one of choice, because a parakeet's daily intake of water is small and because the solution deteriorates rapidly.*

The recommended dosage and treatment schedule caused no side-effects. The concentration and distribution of antibiotic in the organs were the same if the drug was given continuously or on an interrupted schedule. The drug stored in the spleen, kidneys, and liver assured adequate antibiotic levels while the birds were being treated. The treatment has rendered the parakeets noninfectious, and in approximately 98% of the birds properly treated the organs were found to be free from virus. One month after termination of the therapy, aviaries comprising several thousands of parakeets were freed from psittacosis, as proved by systematic examinations of the F_1 to F_4 generations. Since 5 to 20% of the immature parakeets offered for sale may be infected, parents are advised to purchase psittacine birds from aviaries or dealers who sell properly treated birds or who obtain their birds from breeding stocks proved free from psittacosis infection by laboratory tests. Until infection-free parakeets are made available by the trade and properly certified by the health authorities, the keeping and fondling of these pets constitutes some risk to children and perhaps even more risk to older members of a household.